MEMOIRS OF THE SOCIETY FOR ENDOCRINOLOGY
No 7

SEX DIFFERENTIATION AND DEVELOPMENT

Proceedings of a Symposium held at the Royal Society of Medicine Wimpole Street London on 10 and 11 April 1958

Edited on behalf of the Society for Endocrinology by
C R AUSTIN

CAMBRIDGE
AT THE UNIVERSITY PRESS
1960

PUBLISHED BY
THE SYNDICS OF THE CAMBRIDGE UNIVERSITY PRESS

Bentley House 200 Euston Road, London NW 1
American Branch 32 East 57th Street New York 22 N Y

MADE AND PRINTED IN GREAT BRITAIN BY
ADLARD AND SON LIMITED BARTHOLOMEW PRESS DORKING

PREFACE

The Symposium on Sex Differentiation and Development the Proceedings of which constitute this Memoir was arranged by the Society for Endocrinology and was so designed as to bring together authorities in several different disciplines

To advance the frontiers of knowledge an effective strategy should first establish communications between distantly separated salients and in this way yield new perspectives on the intervening ground that remains to be won Accordingly, it was decided that the subject-matter of the Symposium should range as widely as possible should deal with single cells as well as complex organisms with structure and function including behaviour and with both endogenous and exogenous influences Such an ambitious plan of campaign was clearly not possible of execution in detail in the time available but its adoption seemed justified because it offered unusual possibilities of stimulating and informative reconnaissance

The broad plan of the Symposium was developed in committee with Professor F T G Prunty Dr J A Loraine and Dr W Klyne and the details were filled in with the very welcome help of discussions with Dr M W H Bishop and advice from several people especially Dr A S Parkes Dr A U Smith Dr G E W Wolstenholme and Dr B Lacey For their skilful conduct of the Symposium grateful acknowledgment is made to the four Chairmen Dr A S Parkes Professor J D Boyd Professor F W Rogers Brambell and Professor E C Amoroso Sincere thanks are due also to Dr P Eckstein for aid and guidance in the editing of this Memoir

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A S PARKES C B E F R S

Chairman s introduction

The Society for Endocrinology organizes each year a symposium on some subject immediately related to the interests of the Society In the past these symposia have dealt with strictly endocrinological subjects such as hormones in relation to obesity and methods of administering hormones This year a much wider field has been selected and the papers to be presented cover ground ranging from bacteria to mammals and biophysics to anatomy The thread binding together these varied topics can readily be seen from the programme it is sex in many guises and many contexts

This symposium indicative of the wide interests of the Society will take us far outside the boundaries of endocrinology even on the widest definition of that word Nevertheless we shall no doubt hear that hormones are a dominating factor in sexuality not only in vertebrates but in more than one phylum of invertebrates The sexual endocrinology of the Crustacea for instance always of interest since the work on parasitic castration seems to become more fascinating and even more fantastic every day and it is salutary to consider how our knowledge of endocrine effects would have developed had it been based on crustaceans rather than on mammals and birds We may indeed congratulate ourselves that in the animal world the complexities of sexuality seem to be inversely rather than directly proportional to the size of the organism The crustaceans however have no monopoly of the curiosities of invertebrate crinology Among the insects an entirely novel principle appears the use of a secretion not for the integration of the individual but for the integration of a population of individuals Whether this type of organization should properly be regarded as endocrinological or exocrinological is not important The concept is awesome and it is fortunate that the use of queen substance to maintain all other females in subjection as sexless workers appears at present to be restricted to insects

I have already indicated that endocrinology does not exhaust the subject matter of this symposium We shall also hear of such diverse matters as sex in bacteria the possibilities of separating X- and Y-spermatozoa in mammals recent work on mammalian oocytes and not least of sex chromatin in man and of the curious diagnoses made with its aid

The selection of this theme we owe to Dr Austin the Programme Secretary of the Society who rightly regards sex as an important matter Moreover Dr Austin has been responsible for the hard work and careful planning inevitably associated with the organization of a successful symposium and the success of the present meeting is not I think in doubt

In the past the Society has been fortunate in securing the participation in its symposia

of distinguished endocrinologists from abroad This occasion is no exception, and we have with us today Dr M Klein of Strasbourg, Professor A Jost of Paris, and Dr W P U Jackson of Cape Town, to all of whom we extend a most hearty welcome to this country and to the symposium

SEX DETERMINATION AND CASTE DIFFERENTIATION IN THE HONEYBEE *(APIS MELLIFERA)*

By C G BUTLER

Over 100 years ago Dzierzon [1845] stated his well-known theory that unfertilized eggs of the honeybee always give rise to males—drones—whereas fertilized eggs always give rise to females which may become either workers or queens depending upon the manner in which the larvae concerned are fed by the worker members of their colony Dzierzon suggested that a normal mated queen can lay either a fertilized or an unfertilized egg at will and that the kind of egg she lays depends on the kind of cell—worker queen or drone—in which she is about to lay

The Dzierzon theory has, of course become well established although it is now known that females can sometimes develop from unfertilized honeybee eggs In fact in two races of honeybees the South African Cape bee (*Apis mellifera capensis*) and the Tunisian bee (*A mellifera intermissa*) it has been reported that both queens and workers are frequently reared from unfertilized eggs [Jack 1916 Gough 1928] An American worker Mackensen [1943] has also demonstrated that such impaternate females occasionally occur in several races of European honeybees and he succeeded in rearing queens as well as workers from such unfertilized eggs The mechanism by which such impaternate females are produced in the honeybee is unknown but Ruttner & Mackensen [1952] have suggested that perhaps the mechanism is similar to that which is believed to occur in the parasitic wasp *Habrobracon* in which Speicher & Speicher [1938] have obtained cytological evidence indicating that they probably arise from tetraploid tissue in the ovaries Perhaps the Cape and Tunisian honeybees tend to have such tissue in their ovaries and as a result of reduction the egg becomes diploid and consequently develops into a female without fertilization

According to Nachtsheim [1913] and various other workers the honeybee sperm has sixteen chromosomes and the fertilized egg thirty-two

Two theories of sex determination in the honeybee have been put forward In the first Manning [1949–50] has claimed that sex determination is dependent upon the presence of a sex chromosome that is lost in the development of the sperm According to his theory both male and female possess only a single sex chromosome although the female has twice as many autosomes as the male He supposes that during the formation of the ovum differential maturation results in the sex chromosome always remaining in the nucleus of the ovum with the result that a mature ovum contains fifteen autosomes together with a single sex chromosome and if unfertilized gives rise to a male On the other hand, fertilized eggs contain thirty autosomes and a sex chromosome and develop into females However Sanderson & Hall [1951] have subsequently confirmed their previous finding of sixteen chromosomes in the male and

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thirty-two in the female, and Ris & Kerr [unpublished observations quoted by Ruttner & Mackensen, 1952] have shown that Manning's sex chromosome does not stain with Feulgen, although it does so with haematoxylin and they have therefore, concluded that it is a nucleolus and not a sex chromosome at all

Some further evidence against Manning's scheme is provided by the gynandromorph honeybees studied by Rothenbuhler Gowen & Park [1951], who claim to have shown that the male tissue of these gynandromorphs was produced by the entry into the ovum of supernumerary sperm Since, on Manning's hypothesis, maleness is due to a sex chromosome which is not contained in the sperm, and the effect of the autosomes in the sperm is to make the egg female supernumerary sperms could only make the zygote still more female

The other theory of sex determination in the honeybee has been put forward by Mackensen [1951] Its theoretical mechanism resembles that shown by Whiting [1940 1943] to exist in *Habrobracon* Mackensen suggests that in the honeybee a series of sex alleles exist that give female characteristics when heterozygous and are lethal in the homozygous conditions a viable male only being produced from the unfertilized haploid egg His evidence in favour of this theory lies in the rapidity with which on close inbreeding the viability of the eggs laid diminishes towards 50%

Whilst in our own bee breeding at Rothamsted some reduction in viability has been observed on close inbreeding we have at present inadequate data on which to decide for or against Mackensen s theory

The ability of worker honeybees to rear both queens and workers from fertilized eggs has long formed the basis of practical queen rearing by beekeepers and there is no possible reason to suppose that differentiation of the queen and worker castes is determined genetically as it has been shown to be in some of the so-called stingless bees of the genus *Melipona* [Kerr 1946] Caste determination in the honeybee is determined in the feeding of the female larvae concerned

It has been shown experimentally that it is essential for differential feeding to begin before the larva is 3 days old if a perfect queen is to result although queens with a number of worker-like characteristics can be produced from older larvae

Two principal theories to explain caste determination have been put forward In the first it is suggested that the quality of the food received by a larva acts as the determining factor and in the second that it is the quantity of the food received that matters

According to the qualitative theory differences occur in the brood food (which consists partly of a secretion rich in protein of the pharyngeal glands of the worker bees) fed to the larvae of queens and workers after the first 24 hr or so of larval life [von Rhein 1933] But analyses that have been carried out by various workers give very contradictory results and this has led Haydak [1943] and others to conclude that brood food varies in composition quite fortuitously, and that such variations as occur cannot be responsible for caste determination

Having decided that the quality of the food was unlikely to be the responsible factor in caste determination Haydak considered that it must be attributable to differences in

the quantities of the essential nutrients supplied to and consumed by worker and queen larvae respectively He pointed out that, until about the 3rd day of life all larval honeybees in prosperous colonies receive an excess of food but that subsequently while the queen larvae in their large cells continue to be supplied with more food than they can eat the worker larvae in much smaller cells only receive relatively small quantities of food from time to time The result is that the queen and worker larvae grow at approximately the same rate for the first day or two but subsequently whereas the queen larva surrounded by an abundance of food continues to grow rapidly the much more frugally fed worker larva grows more slowly Haydak [1943] pointed out that even after her cell has been sealed a queen larva continues to feed upon the surplus of brood food in the bottom of her cell whereas a worker larva having no such source of food, cannot feed any more once her cell has been sealed, and actually loses weight

In order to test his hypothesis Haydak removed the larvae from queen cells that were either just about to be sealed or had just been sealed, so that they could not eat any more food. Most of the larvae that he treated in this way died in the pupal stage but he reported that seven of these pupae possessed worker rather than queen characteristics while several others were intermediate in form between queens and workers Nine adults were obtained all except one of which were normal queens the exceptional individual being intermediate between a queen and a worker Haydak reported that the average initial weight of those of the larvae that developed into queens was 14% greater than that of larvae developing into individuals with worker or intermediate characteristics

From Haydak s results it certainly appears likely that continuous liberal feeding of those larvae that are destined to become queens plays an important role in their differentiation However von Rhein [1933] who in the laboratory fed female larvae very liberally with brood food taken from queen cells failed to obtain the queens one would have expected if Haydak s hypothesis were correct Indeed his failure to produce queens in this way led von Rhein to suppose that some unstable, differentiating substance is fed by worker bees to those larvae that are destined to become queens and that this fugitive substance had either been destroyed (or perhaps lost during storage) in the brood food he took from queen cells and fed to his larvae

Simpson [1957] has also shown that abundant feeding alone even when it is carried out by worker bees themselves is insufficient to cause a female larva to develop into a queen.

Recently Weaver [1955 1957] has reported the results of some experiments similar to those of von Rhein [1933] in which he fed young female larvae taken from worker cells on abundant brood food freshly collected from queen cells containing larvae of approximately the same ages as the experimental ones In these circumstances queens were produced On the other hand when similar larvae were fed abundantly with brood food collected from queen cells and stored for some time only workers were produced. These results clearly fail to support Haydak s conclusion, as the experimental larvae were continuously supplied with a superfluity of food so that quantitative starvation could not have been the determining mechanism On the other hand they

strongly support the conclusion of von Rhein [1933] that some substance (or substances) contained in the food fed by the workers to the larvae in queen cells controls their differentiation into queens, and that at least some essential part of this substance is either highly labile or else is no longer available to larvae after the food has been exposed to the air for some time even in a refrigerator

It seems probable, therefore that in order that a given female larva may give rise to a queen she must continually receive liberal supplies of fresh brood food in which the differentiating substance is still active Furthermore, in order that a normal queen may be produced the larva must be fed on this diet from at least the 3rd day of life onwards [Weaver 1957]

Now, in a normal colony of honeybees the ovaries of the workers remain undeveloped and no eggs are laid by them and except under special conditions the workers do not attempt to rear any new queens But if a colony loses its queen perhaps through accident or disease, two things normally occur First, within a few hours the workers will have modified one or more worker cells containing young female larvae to form emergency queen cells and by special feeding of these larvae will cause them to develop into queens All being well one of them will replace the queen that was lost the others will be destroyed Secondly the ovaries of the adult workers particularly those of the younger ones will develop slightly [Hess 1942] Normally, when a queen has been successfully produced, this process is reversed but should there be no larvae present from which the workers can rear a new queen or should they fail to do so for some other reason then the workers ovaries continue to develop until useless drone-producing eggs are laid It is clear therefore that normally the presence of a queen is sufficient to inhibit both development of the workers ovaries and the production by them of further queens The presence of open, occupied queen cells has a similar inhibiting influence [Butler 1957a]

It has recently been demonstrated that development of the worker ovary is normally inhibited by a remarkably stable substance that the workers of a colony obtain by licking the body of their queen [de Groot & Voogd 1954 Pain 1954], and Butler [1954 1956 1957b] has shown that this substance is passed from bee to bee in regurgitated food Furthermore, either the same or some very similar substance called queen substance' by Butler [1954] that is collected in the same way by the workers from their queen and also distributed in regurgitated food is responsible when in sufficient supply for inhibiting workers from rearing further queens [Butler 1954 1957c Butler & Gibbons 1958 Simpson 1958] It seems probable that a single substance is involved and biologically effective extracts have been obtained both in acetone and in alcohol [de Groot & Voogd 1954 Butler 1957b Butler & Gibbons 1958]

The existence of similar ovary-inhibiting substances has recently been demonstrated by Bier [1954] in several species of ants and Luscher [1953 1956] and others have shown that certain queen termites produce a substance that inhibits the development of supplementary reproductives in their colonies

Again Carlisle & Butler [1956] have obtained evidence suggesting that honeybee queen substance is interchangeable with a substance found in the sinus glands in the

eyestalks of prawns (*Leander serratus*) which inhibits development of their ovaries and Butler [unpublished] has obtained evidence indicating that the inhibitory substance produced by at least some species of queen ants is interchangeable with honeybee queen substance It looks indeed as if certain inhibitory substances produced by the queens of at least some social insects and which play important roles in the organization of their colonies are to some extent interchangeable Perhaps they are chemically similar this we do not know as none of them has yet been isolated and identified

Dr Callow and Miss Johnston of the National Institute for Medical Research and the author are trying to identify the active principle in queen substance We have also tested a number of steroids to see whether they produce similar effects on bees So far we have been able to mimic the action of queen substance in inhibiting ovary development in worker bees with androsterone but have not been able to demonstrate that this substance prevents them from rearing queens

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COMMENT

Peacock I should like to draw your attention to certain long-standing problems of sex in invertebrates For example how far the theories of sex determination in the two hymenopterans the honeybee and *Habrobracon* discussed by Dr Butler, can be applied to other arrhenotokously parthenogenetic organisms, e g saw-flies, ants and other Hymenoptera rotifers thrips remains unknown

Regarding sex determination in other insects two particular cases in the Lepidoptera are of interest Goldschmidt [*Bibl genet Lpz*, 1934 **11**, 1] obtained intersexes of the gypsy moth by crossing different geographical races which differed in the strength of their female- and male-determining factors More recently Seiler [*Experientia* 1949 **5** 425] obtained different results with *Solenobia* moths For example a tetraploid female *of a parthenogenetic race crossed with a male of a diploid race gave triploid intersexes* Goldschmidt held that all members of a given hybrid brood showed the same degree of intersexuality and that the degree of intersexuality was finally attained only after the competing female- and male-producing determining factors had reacted over a certain period of time In contrast Seiler found all grades of intersexes in the same brood and no switch-over of sex during the larval and later stages each individual intersex beginning and remaining at the same fixed grade Seiler therefore suggests that there operate phenotypic factors at present unknown

In certain Crustacea other than the decapods to be dealt with by Dr Carlisle as well as in other invertebrates we find alternation between the parthenogenetic and bisexual modes of reproduction (heterogony) Environmental factors certainly determine this alternation By refined culture techniques in which the effects of food light temperature excretory products etc were tested von Dehn [*Zool Jb* 1937 **58** 241 *Naturwissenschaften* 1950 **37** 429] and Buchner [*Z indukt Abstamm VererbLehre*, 1936 **72** 141] respectively for the crustaceans *Daphnia* and *Moina* and certain rotifers found that the females of a long-continued parthenogenetic culture can be switched to male production the main factor involved being the quality of food the fatstuff content of the latter being important in *Moina* Also effective to a certain extent in *Moina* were light deficiency associated with food deficiency and darkness In the gall-midge *Oligarces paradoxus* the larva of which is parthenogenetic (paedogenesis) the switch-over to adulthood and bisexuality is effected by the quantity of food or more strictly by the constellation of environmental factors (age of parent population density etc) that together influence the food available [Ulrich *Naturwissenschaften* 1940 **36** 569 **37** 586] In the bean aphis where a succession of parthenogenetic generations occurs on alternate host-plants Davidson [*Ann appl Biol* 1929 **16** 104] showed that after prolonged parthenogenetic reproduction sexual females and males could be produced by reducing the amount of light or by lowering the temperature

No hereditary factors determining sex have so far been observed by von Dehn Buchner nor Ulrich in their experimental material How the environmental factors mentioned produce their effects of sex change or change in the method of reproduction by influencing chromosomal and/or endocrine processes is unknown

SEXUAL DIFFERENTIATION IN CRUSTACEA MALACOSTRACA

By D B CARLISLE

The field of study about which I am going to talk today must be so unfamiliar to most of you engaged in vertebrate endocrinological research that I feel it may be worth while to present briefly the whole picture of the hormonal control of sexual differentiation in Crustacea of the Order Malacostraca so far as it is known rather than describe in detail my own work on the subject The Malacostraca are the higher Crustacea and include such forms as crabs lobsters shrimps and sand-hoppers Apart from my own investigations most of the research involved has been performed by French workers and I would refer particularly to the recently published thesis of Mme H. Charniaux-Cotton [1957] who has brilliantly elucidated much of the sexual endocrinology of the sand-hopper *Orchestia*

Four organs have been shown to produce hormones influencing the sexual development in Crustacea The first to be so implicated was the ovary As early as 1926 Haemmerli-Boveri castrated Crustacea by irradiation as others also did in the years just before the war [Roux 1933 Callan 1940 Knowles & Callan 1940] Takewaki & Nakamura [1944] and Charniaux-Cotton [Charniaux 1952 1953*a* *b* Charniaux-Cotton 1954*a* *b* 1956*a* *b* 1957] castrated Crustacea by surgical means a most difficult technical feat All are agreed that the only effect is the non-development of the secondary brooding characters—the pregnancy characters as it were—of the gonadectomized females Castrated males are not affected in any way not even in behaviour Both males and females after castration develop all the appropriate secondary and accessory sexual characteristics Hence the control of the differentiation of sexual characters in Crustacea does not lie in any hormonal secretion of the gonads We must look elsewhere but first it should be mentioned that it is the ovary undergoing vitellogenesis that secretes the hormone responsible for the development of the brooding characters

The organ most recently implicated in the sexual differentiation of Crustacea is the gland first described without a name by Charniaux-Cotton [1954*b*] adjacent to the vas deferens in *Orchestia* I have called it the vas deferens gland [Knowles & Carlisle 1956] while Charniaux-Cotton [1956*c*] has referred to it as the glande androgene The former name seems preferable for it is customary to name an organ after its position and anatomical relationships rather than its presumed function Charniaux-Cotton like myself has also observed the gland in decapod Crustacea. In all it lies in or alongside the wall of the vas deferens It betrays histological signs of secretion which vary with the sexual state of the animal We owe most of our knowledge of its functioning to Charniaux-Cotton who has experimented exclusively upon *Orchestia* Briefly she finds the gland responsible for the entire development of the male characters both primary and secondary Removal of both glands from males whether castrated or not

Key to the Circulatory Diagrams

1	Arterial blood (fully saturated)	1
2	Arterial blood with some admixture of venous blood but not a sufficient amount of reduced hemoglobin to give visible cyanosis	2
3	Arterial blood with a sufficient amount of reduced hemoglobin to give visible cyanosis	3
3x	Venous blood with but a slight admixture of oxygenated blood (This combination of shading is used in only one diagram in Volume II in which there is increased cyanosis in the upper extremities as compared with that in the lower extremities)	3x
4	Venous blood	4

proximately 70 per cent saturated that in an infant with a complete transposition of the great vessels may contain little or no oxygen No attempt has been made to indicate the actual saturation of the venous blood or that of the mixed venous and arterial blood Hence the circulatory diagrams show only the *relative* difference between venous blood and arterial blood whether the arterial blood is fully oxygenated, whether it contains such a small amount of venous blood that there is no visible cyanosis, or whether the admixture of venous blood with arterial blood is sufficient to produce visible cyanosis As in the first edition the word venous arterial is used to denote the flow of blood from the venous to the arterial circulation and the term arteriovenous is used to denote the flow of blood from the arterial to the venous side

All x rays were taken at seven feet The photographs of the x rays have been retouched in order to make the final plates true reproductions of the originals Outlines have been sharpened but no new lines added

Angiocardiograms however are not taken at seven feet therefore there is distortion in the size of the heart and the great vessels As in the x rays no new lines have been added, but the angiocardiograms too have been sharpened so as to clarify the outlines of the various chambers Moreover, it should be remembered that the author has selected classic examples and insofar as possible she has adhered to her principle with the angiocardiograms as with the x rays of

showing examples in which the diagnosis has been proven at operation or at autopsy In many instances it is not easy to identify all the outlines with cer tainty, under such circumstances, emphasis should always be placed on the clear cut, unquestionable findings

All x rays and fluoroscopic studies are discussed as if the patient were facing the observer Therefore, throughout this book, right refers to the patient s right and left refers to the patient s left Hence, the term anterior posterior position is retained In all illustrations the patient s right is on the left hand side of the page Throughout this book the primary consideration is to present the patient as he presents himself to the physician

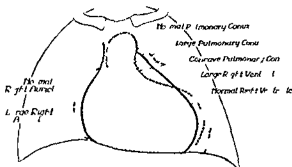
It is to be remembered that all x rays and all angios are two dimensional images of three dimensional objects The drawings of the normal x ray contours are based upon the work of many persons—principally Evans Palmer, Bedford, and Parkinson in England, Assmann in Austria, and Roesler formerly of Aus tria and now of the United States—and upon various models and autopsy studies The drawings of the contours of abnormal hearts are based on the author s observations All our examinations have been made on living subjects Infants have been examined in the recumbent position, children and adults in the erect position The changes in the contour of the heart have been recorded during life, and the significance of the changes has been checked at the autopsy table The dotted lines show the approximate contours of the chambers of the heart These lines are dotted as they are only estimates the actual boundaries of the chambers of the heart cannot be visualized upon fluoroscopy

In Volume I a chapter on the basic information to be derived from angiocar diography and cardiac catheterization has been added Dye dilution curves are not discussed as the author has had no experience with them and she has ad hered to her principle of basing the book on her own experience Furthermore this book is not intended to be one on the physiology of malformations of the heart Left heart catheterization is but briefly mentioned It will probably be used with increasing frequency The basic principles of the analysis of the informa tion are the same as those of right heart catheterization

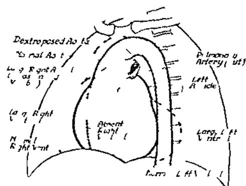
In Volume II a brief discussion of the physiology and the hemodynamics of each malformation has been added to each chapter and the findings on angio-cardiography and cardiac catheterization in each of the specific malformations are discussed It should be remembered that both tests are of greatest value when undertaken to elucidate a specific point Nevertheless we must not be blind to

the unexpected As in most things a balance must be maintained between the search for the specific and an objective analysis of what is actually found

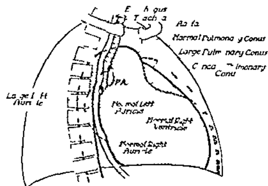
The surgical correction of cardiovascular defects is discussed from the clinical aspect namely, the indications and contraindications for operation and the amount of benefit to be derived therefrom No attempt is made to discuss surgical technique, as that is the province of the surgeon, not the clinician This book *is written for the benefit of the clinician and the author hopes also for the benefit* of the patient



Anterior posterior position



Left anterior-oblique position



Right anterior-oblique position

Key to the contour of the infant heart

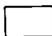
Diagram A

Normal circulation

In the normal circulation the blood from the right auricle passes into the right ventricle and out by way of the pulmonary artery to the lungs where it is oxygenated The oxygenated blood is returned from the lungs by the pulmonary veins to the left auricle thence it passes to the left ventricle and out by way of the aorta to the systemic circulation The blood from the head and upper extremities is returned by the superior vena cava to the right auricle and that from the trunk and lower extremities by the inferior vena cava to the same auricle There the cycle starts again

Although the foramen ovale may not be completely sealed inasmuch as the valve opens from right to left it always remains closed unless the pressure in the right auricle becomes higher than that in the left auricle Only if the pressure in the right auricle becomes greater than that in the left auricle is there a right to left shunt So long as the valve is intact the shunt is never left to right

Diagram A


Arterial blood (fully saturated)


Venous and arterial blood
Cyanosis visible


Small admixture of venous blood
No visible cyanosis


Venous blood

CONGENITAL MALFORMATIONS OF THE HEART

Volume I

CHAPTER I

EMBRYOLOGY, ETIOLOGY, BASIC PRINCIPLES OF ANALYSIS AND FETAL CIRCULATION

MALFORMATIONS of the heart follow specific patterns just as other malformations do As all harelips and all cleft palates follow a definite pattern so the same malformation of the heart in each instance alters the structure of the heart and the course of the circulation in much the same manner Furthermore, just as there are all gradations in the severity of a harelip or a cleft palate, so with each and every malformation there are gradations in the severity of the abnormality The ductus arteriosus which remains patent may be large or it may be small The pulmonary stenosis may be extreme or it may be slight Indeed, in almost every type of malformation the abnormality may be so slight as to cause little or no strain upon the heart or so severe as to be compatible with life for a short time only The variation in the severity of the abnormality affects both the symptoms produced by the malformation and the prognosis

Embryological studies indicate that malformations result from developmental errors either arrests or retardations in the growth of the embryo at some specific point or some abnormality in the rate of growth or differentiation of the various parts of the embryo Malformations may be caused by defects in the egg or by faulty environment Corner states that the identical malformation may result from a bad egg in a good environment as from a good egg in a bad environment [1] The experiments which prove this point have been performed only on lower animals There is, however no reason to believe that the human embryo differs in this respect from all other embryos or that the human heart differs from other organs of the human body

EMBRYOLOGY

Virtually the entire development of the heart occurs between the twenty first and the fortieth day of embryonic life During this brief period the embryo grows from 3 mm in length to approximately 15 mm crown rump length For a detailed discussion of the embryology of the heart, the reader is referred to the works of Streeter, Hamilton, Boyd and Mossman [3] Patten [4] and others

It is important to remember that the entire embryo is simultaneously under

going rapid differentiation Because of the simultaneous growth of the various organs, Streeter introduced the conception of horizons , that is, he recorded the extent of the development of the various organs seen in embryos of successive ages and sizes Each horizon covers a two day period in the development of the human embryo The salient features in the development of the heart may be summarized as follows

According to Streeter during the first three weeks of life the embryo is so minute that all the cells can receive their nutrition by simple diffusion As soon as the growth of the embryo is such that this is no longer possible, that is, at *about the twenty first day of embryonic life, the aggregation of cells destined to* form the heart begins to differentiate near the cephalic end of the embryo Shortly thereafter when the embryo is only 2 to 4 mm in length the heart begins to pulsate At this stage, which Streeter terms Horizon XI the heart passes caudo cranially through the pericardial sac and is fixed to the pericardial wall only at its venous entrance and at its arterial outlet The portion of the tube which is free from the pericardial sac grows more rapidly than does the peri cardial cavity Consequently it is bent first in a U shaped loop and then in an S shaped curve as shown in Figure 1–1 This loop, which involves mainly the ventricles and the bulbus portion of the heart, is known as the bulboventricular *loop*

The ventricle bulges forward and to the left and swings back to the right to form the bulbus cordis (see Figure 1–2) By the fifth week of embryonic life the anlage of the various chambers can be discerned Shortly thereafter a muscular ridge appears in the floor of the bulboventricular cavity, the two portions of the ventricle dilate, and the ventricular septum starts to develop (see Figure 1–3) By this time the embryo is approximately 10 mm in length

While the bulbus cordis and the ventricular loop are developing the venous end also undergoes rapid differentiation The atrium lies behind and above the ventricles and the atrioventricular canal leads into the common ventricle The auricles* expand rapidly and by the time the embryo is 4 mm in length, that is, at Horizon XIII the beginning of the septum primum can be discerned (see Figure 1–4) In the next horizon (see Figure 1–5) the right and left sinus venosus have become fused and open into the right side of the common atrium By the fifth week of embryonic life, when the embryo is approximately 7 mm in length and thirty days of age, that is, at Horizon XV, the superior cardinal vein

*The word auricle instead of atrium is used throughout this book to describe the differentiated cavity as it now is a generally accepted term in cardiology

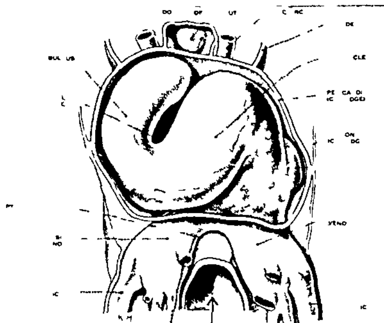


FIGURE 1–1 S shaped curve of the embryonic heart

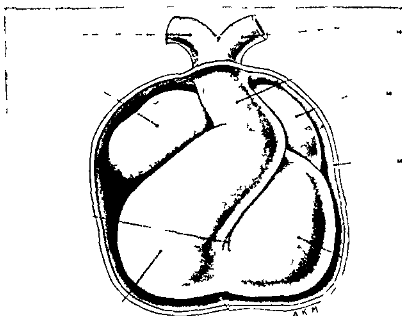


FIGURE 1–2 Ventral aspect of the heart of a human embryo 5 mm crown rump length

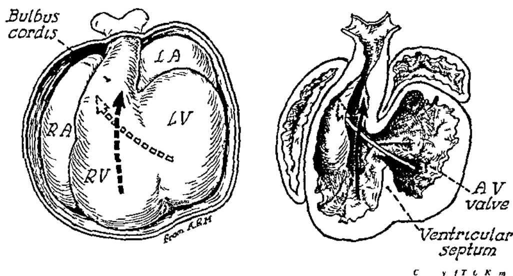


FIGURE 1-3 Section through the ventricular septum and bulbus cordis in a human embryo 8.8 mm in length. Adapted from a drawing by A. K. M.

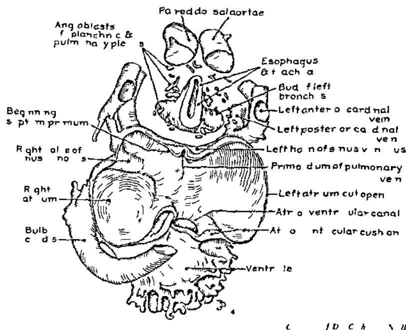


FIGURE 1-4 Human embryo 4 mm in length, 26 days of age (Horizon XIII). Anterior superior view showing expansion of right and left atria and atrioventricular canal leading to a common ventricle.

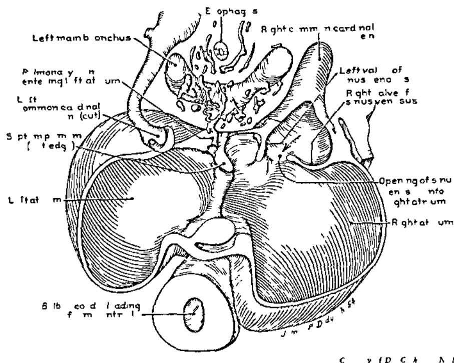
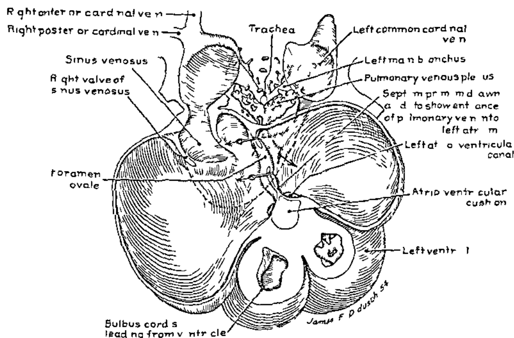


FIGURE 1–5 Human embryo 6 mm in length 28 days of age (Horizon xiv) Posterior inferior view showing that the septum primum now separates the two auricles

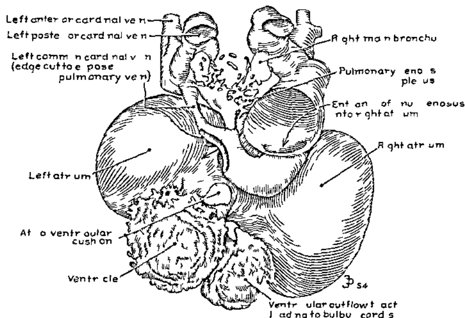
opens into the right auricle and the single pulmonary vein opens into the left auricle and the left common cardinal vein can be seen to course posteriorly to the right to open into the coronary sinus This stage in the development of the heart is shown in Figure 1–6 Two days later at Horizon xvi the opening at the base of the auricles that is the ostium primum, has closed and that higher up in the auricular septum namely the ostium secundum has opened

As the auricular and ventricular cavities expand the atrioventricular canal becomes the atrioventricular ring At about this time the endocardial cushions of the atrioventricular canal divide to form the anlage of the tricuspid and the mitral valves By the thirty sixth day when the embryo is approximately 14 mm in length the mitral and tricuspid valves lead from the left and right atria into their respective ventricles

As previously mentioned, the heart begins to pulsate while it is but a primitive tube Thus, from the very beginning while the two ventricles are forming the blood is being pumped through the heart At this stage in the development



Anterior superior view



Posterior inferior view

FIGURE 1-6 Human embryo 7 mm in length 30 days of age (Horizon XV) Superior cardinal vein opens into the right auricle Single pulmonary vein opens into the left auricle

of the heart the bulbus cordis leads into a common truncus Nevertheless, as the ventricle contracts the posterior portion of the ventricular loop, which is destined to become the left ventricle, directs the blood forward toward the anterior portion of the bulbus cordis from which the aorta is destined to arise the anterior portion of the common ventricle, which is destined to become the right ventricle, directs the blood posteriorly in the direction of the future pulmonary artery as shown by the arrows in Figure 1-3 Thus, at an early stage in the development of the heart the forces are set in motion for the separation of the streams of blood which subsequently flow to the body and to the lungs

While the heart is forming, the blood vessels begin to make their appearance everywhere, the vascular bed is forming the lung buds are developing the liver is being differentiated and so forth The relation of the development of the various organs to the development of the heart is shown in Figure 1-7

The vascular bed, including the aortic arches and the aortic sac from which

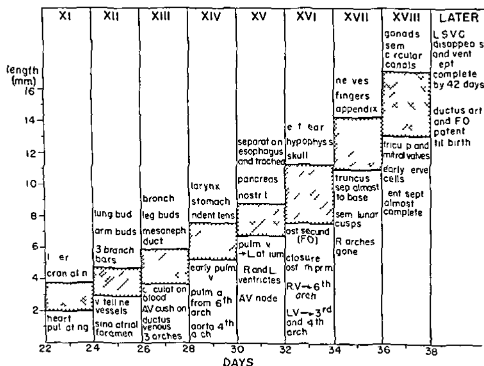


FIGURE 1-7 Developmental horizons of the human embryo Neill s modification of Streeter s chart

the great vessels are derived, is undergoing differentiation at the same time that the heart is being formed Streeter has repeatedly emphasized that the vascular bed of the embryo is extremely rich and blood vessels are laid down according to the lines of stress and strain Congdon[5] has shown that the arterial end of the heart at first lies below the cranial end of the pharynx and later shifts backward to occupy its ultimate position within the chest As the heart shifts posteriorly, the aortic arches develop in regular order from before, backward, these arches connect the aortic sac and the primitive heart with the paired dorsal aortae The chief cause of the disappearance of the first and second aortic arches seems to be the shift of the blood stream to the more caudal arches which occurs in conjunction with the caudal movement of the heart and aortic sac Normally, the division of the current of blood which flows forward to the head and that which is directed to the trunk and lower extremities occurs between the third and fourth aortic arches The dorsal aortae approach one another and become fused from behind forward *Normally, it is the fourth left aortic arch which forms the arch* of the aorta and establishes the permanent connection between the heart and the posterior descending aorta The fifth aortic arches are inconstant, transitory vessels which atrophy at an early date The sixth aortic arches extend, as do the fourth aortic arches, from the aortic sac to the dorsal aortae It is from the sixth aortic arches that the pulmonary arteries develop During the fifth week of embryonic life the sixth right aortic arch distal to the pulmonary artery atrophies and disappears the sixth left aortic arch distal to the pulmonary artery persists as the ductus arteriosus and leads to the descending aorta

Simultaneously with the development of the heart and great vessels the lung buds develop These can be detected by the time the embryo is 3 to 5 mm in length that is by the twenty sixth day As everywhere there are rich vascular channels around these primitive lung buds According to Neill,[6] in the 6 mm human embryo these channels fuse together and form a single vessel which meets an outpouching from the left auricle (see Figure 1-5) Thus at the very beginning the pulmonary veins open into the left auricle by a single vein this vessel bifurcates and each branch in turn divides again As the auricle expands these four branches of the pulmonary veins become incorporated into the wall of the left auricle

Thus as previously mentioned virtually the entire development of the heart and great vessels takes place between the twenty first and the fortieth day of embryonic life By the second month of embryonic life the heart has assumed the adult configuration Thereafter the heart muscle continues to differentiate and

to condense The musculature of the heart does not assume the adult structure until at or near term At birth of course, the ostium secundum and the ductus arteriosus are still patent

RELATION OF MALFORMATIONS TO EMBRYOLOGICAL DEFECTS*

Ectopia cordis represents an arrest in the development of the heart of such a nature that it fails to complete its descent into the thorax Little wonder that such a severe anomaly which must completely alter the forces of stress and strain, is usually associated with some gross and bizarre cardiac anomaly Such was the situation in the only ectopia cordis the author has ever seen

Dextrocardia occurs when there is a reversal in the direction of the primitive cardiac loop with the result that the apex of the heart lies on the right side and not on the left

Anomalies of the aortic arch are due to variations in the development of or to atrophy of one or more of the primitive arches For example a right aortic arch is due to persistence of the fourth right aortic arch and atrophy of the corresponding left aortic arch A double aortic arch results when both the right and left arches persist A *truncus arteriosus communis* is explicable on the basis of abnormality in the growth of the aortic septum and the manner in which it develops in relation to the ventricles as well as to the pulmonary artery *Complete or partial rotation of the great vessels* occurs when there is an abnormality in the direction or in the degree of rotation of the aortic septum or in the manner in which it meets the bulbar septum Since both the aorta and the pulmonary artery originate from the bulbus cordis, it is not surprising that in such abnormalities it is relatively common to find that the aorta arises in part from the right ventricle

Malformations of the pulmonary venous return are explicable on the basis of abnormalities in the development of the pulmonary veins and the manner in which these veins connect with the growing heart

Subaortic stenosis is believed to be due to a failure of the bulbar septum to atrophy whereas *pulmonary stenosis* is thought to be due to an arrest in the growth of the bulbus cordis

Auricular septal defects represent arrests or failures in the growth of the auricular septum

Ventricular septal defects are due either to failure of the musculature which

*A more detailed discussion of this subject is given in the respective chapters dealing with each of the specific anomalies

with a single auricle, and of splenic agenesis[16] with malformations of the great vessels

Although all the above examples could be caused by extrinsic factors acting on the embryo the malformations which are compatible with life frequently re appear in successive generations, as, for example, Marfan s syndrome and the Ellis van Creveld syndrome

Studies on the chromosomal patterns in Mongolian idiots, first undertaken by Lejeune, Gautier, and Turpin[1] and promptly confirmed by others, have demonstrated that these individuals have a small extra chromosome This method of study opens up an entirely new approach to human genetics

The curious sex incidence which occurs in certain malformations must reflect some sensitivity in the development of the heart which is associated with certain chromosomes or genes or whatever ultimately proves to be the basis for the dif ferentiation of the sexes Although the phenomenon is not understood it is well known that there are striking variations in the sex incidence in certain malfor mations For example, coarctation of the aorta is far more common in men than in women it occurs relatively frequently in women with ovarian agenesis, and least frequently of all in normal women Persistent patency of the ductus arteri osus and auricular septal defect of the ostium secundum type are more common in women than in men Ultimately an explanation for these observations will un doubtedly be forthcoming and almost certainly in some way it will be related to the factors which concern the etiology of malformations

Extrinsic factors are also of great importance These factors may affect the embryo by direct penetration or by transmission through the placenta Although the mother s blood and the placenta protect the fetus from many insults certain external factors may penetrate the placenta and affect the growing embryo Obviously, for any substance to injure the embryo it must be operative early in gestation while the heart is forming that is in the first months of intra uterine life Furthermore the noxious agent must be of such toxicity that it is severe enough to injure and not so severe as to kill the tiny embryo Furthermore, if the noxious agent is a foreign substance circulating in the mother s blood it must be of proper size to penetrate the placenta There are, however, a number of sub stances which may be injurious to the embryo

X ray and radiation may seriously injure the fetus by direct penetration Car diac abnormalities may result from such exposure during the period when the heart is undergoing *differentiation that is during the first trimester* Further more it is important to remember that radiation may injure or kill the fetus at

any age, and therefore all such exposure should be avoided as assiduously as is possible

There is great unanimity of opinion among the workers in atomic energy that radiation not only may injure the embryo but also may injure the reproductive organs of either sex in such a manner as to cause sterility or to lead to the production of monsters In brief, radiation may injure a good egg or lead to the production of a bad egg Furthermore, such injury may be transmitted to future generations In this age of atomic energy the danger of injury from radiation is of increasing magnitude and of increasing difficulty to control

Virus infections in early pregnancy affect the development of the embryo Gregg[18] and Swan et al [19] have shown that German measles in the first two months of pregnancy are associated with an extremely high incidence of congenital cataracts and congenital malformations of the heart Indeed, if the infection occurs during the first month of pregnancy, the fetus is defective in nearly 100 per cent of the cases When the infection occurs in the third month of pregnancy, there is a fifty fifty chance that the infant will be normal Infection after the third month of pregnancy apparently carries no liability of injury to the fetus When it is recalled that the entire development of the heart occurs during the first two months of embryonic life, it is readily comprehensible that this is the period during which infection is liable to affect its development The earlier the infection occurs the greater is the probability that the fetus will be abnormal

By far the most common combination of abnormalities which results from a maternal infection by the rubella virus in early pregnancy is microcephaly, congenital cataracts, and persistent patency of the ductus arteriosus This extraordinarily specific developmental abnormality occurs at an extremely early stage in embryonic life This injury which causes the failure of the ductus arteriosus to obliterate occurs long before the aortic arches have developed indeed almost before the primitive cardiac tube can be discerned The specificity of this injury is especially remarkable because the tissue concerned with the obliteration of the ductus arteriosus cannot be detected until the infant has nearly reached term *

Vitamin deficiencies in the diet fed to experimental animals during pregnancy have been shown to produce a high incidence of abnormalities in the offspring of these animals The first such experiments are credited to Hale [0] Since then many experiments of a similar nature have been performed with a wide variety of substances The clinical aspects of such studies have been emphasized by Warkany [1] Such diets are grossly deficient Normally the mother s blood

Personal communication Dr B M Patten

offers protection to the embryo,[1] it remains to be determined whether or not minor dietary deficiencies are of importance to man It is, however, conceivable that prolonged dietary insufficiencies may be a factor in the production of malformations Chronic dietary deficiencies were sustained in concentration camps and may readily occur in countries where famine is common

Many substances given to pregnant animals at specific times have been shown to increase the incidence of malformations in the offspring For a detailed review of the subject, the reader is referred to the report by Kalter and Warkany [0] One of the most interesting of these experiments as regards malformations of the heart is the production of various types of transpositions of the great vessels by the injection of trypan blue into pregnant rats at specific times Fox and Goss have shown the similarity between the transposition complexes produced by this method and those which occur in man

In brief, all these experiments indicate that extrinsic factors and specific alteration in the metabolism of the mother at a specific time during pregnancy may affect the development of the embryo Furthermore, extrinsic factors may be such as to injure both the embryo and its genes *

The Kartagener triad[3] of situs inversus, bronchiectasis, and sinusitis has high familial incidence but notably occurs in a single generation It has been repeatedly emphasized that its occurrence in a single generation points to an environmental rather than a genetic factor

Air travel with the change in atmospheric pressure and the constant vibration of the plane has been questioned as a cause of malformations of the heart If it is a factor, it would be operative only while the heart is developing, that is, during the first trimester

Syphilis and fetal endocarditis once considered so important, are relatively unimportant or non existent factors

BASIC PRINCIPLES IN THE ANALYSIS OF MALFORMATIONS

Inasmuch as a malformation of the heart results from faulty development at some specific point in the formation of the heart, the remainder of the heart develops in as nearly the normal manner as is possible under the altered circumstances Consequently unless there has been an error in the direction or in the

* The fact that specific injury to an embryo may injure the future generations of that offspring gives hope that when these factors are better understood the reverse may be possible namely that by the correction of a fetal abnormality it may ultimately be possible to endow the future generations of its offspring with a sound heredity

degree of the rotation of the primitive cardiac loop, as in cases of dextrocardia or dextrorotation, the malformed heart occupies the same position as the normal heart the apex points to the left, the right ventricle (or what remains thereof) lies anteriorly, the left ventricle lies posteriorly, and the aorta arches over the pulmonary artery and descends upon the left The fact that in the vast majority of instances regardless of the type of the malformation, the heart does occupy its normal position renders it possible to analyze which chambers are enlarged and which are small, this information is of prime importance in the analysis of the nature of the malformation

Any part of the heart or the vascular bed may be affected The abnormality may be slight or it may be great There may be a malformation of one of the chambers or of the great vessels There may be an anomaly of the arterial trunk or of the venous return It is, of course possible to have two or more malformations in the same heart, but by and large this is rare When it does occur each malformation affects the circulation in a specific manner It is the recognition of the clinical features characteristic of each of the different malformations which renders it possible to make the correct clinical diagnosis For this reason, each abnormality is presented as a separate clinical entity No attempt is made to differentiate minute anatomical variations The problem is approached from the clinical angle the diagnosis is made on a broad functional basis

DIFFERENCES IN THE APPROACH TO THE PROBLEMS OF ADULTS AND OF INFANTS

One of the serious obstacles to the correct diagnosis of cardiac abnormalities in infants is that the same methods of diagnosis which have proved useful in the case of adults are often applied to infants In adults the quality the time the location, and the transmission of the murmur are often of great diagnostic aid Anyone who has used these criteria for the diagnosis of the nature of a malformation in infants must admit that accuracy in diagnosis is only in accord with the laws of chance The malformations which can be diagnosed by these findings must wait until the growth and development of the individual have rendered the findings significant In infants although the occurrence of a murmur may suggest an abnormality in most instances the heart is too small, the blood pressure too low and the chest wall too thin for special characteristics of the murmur to be of diagnostic aid

Most of the cardiac malformations fatal in early infancy are associated with alterations in the size and shape of the heart and in the vascularity of the lungs Such changes can be demonstrated by x ray and fluoroscopic studies The use

fulness of these studies is greatest in those cases in which the heart occupies its normal position. If the heart is rotated upon its axis these studies indicate only whether the anterior or the posterior portion of the heart is enlarged, but the assumption that the right ventricle lies anteriorly and the left ventricle posteriorly is no longer justified. Fortunately these cases are rare; in the vast majority of instances the position of the heart is normal. Consequently, in early infancy when murmurs and thrills are of little aid in diagnosis, x-ray and fluoroscopic studies are of great value. This method of analysis is considered in detail in Chapter II.

CHANGES OF CARDIAC CONTOUR WITH GROWTH

The age at which the heart assumes its characteristic size and shape varies with the nature of the malformation. The fundamental shape of the heart is determined during intra-uterine life. The size and shape of the heart at birth depend upon the nature of the malformation and the amount of strain which the fetal circulation placed on the malformed heart. The ultimate size and shape of the heart depend upon the duration of life and the load placed on the malformed heart by the extra-uterine circulation.

Although in the normal circulation the same volume of blood is pumped out of both ventricles, this is no longer necessarily true when there is an abnormal opening between the two circulations. In most malformations the blood which is shunted from one side of the heart to the other is returned to the side from which it was shunted. For example, if the shunt is from left to right, the blood which is shunted from the left side to the right is pumped around the lesser circulation and is returned to the left side of the heart and there the cycle starts again. Similarly, if the blood is shunted from right to left, it is pumped around the systemic circulation and is returned to the right side of the heart. Thus if x equals the volume of the shunt, the volume of blood in one circulation is increased by x and that in the other is decreased by x. Nevertheless, so long as the size of the opening and the relative pressure in the two circulations are constant, *the volume of the shunt will remain constant*. The volume of the shunt determines the amount of the load, which in turn determines the degree of cardiac enlargement. Most such malformations place a constant load upon the heart; once the heart has adjusted to the load, further increase in the size of the heart is proportional to the growth of the individual. Such malformations do not cause progressive cardiac enlargement.

To analyze the strain placed on the heart by a malformation requires a

knowledge of both the normal fetal circulation and the changes which take place at birth

NORMAL FETAL CIRCULATION

The fetal heart differs from the adult heart both in structure and in function During fetal life the lungs do not function for the oxygenation of the blood The entire exchange of nutrition and waste products and also the exchange of oxygen and carbon dioxide takes place in the placenta The sole function of the heart is to pump the blood around the body of the fetus If the heart is unable to do this the fetus dies

The structure of the fetal heart is adapted to the requirements of fetal life The flow of blood to the lungs is minimal The foramen ovale and the ductus arteriosus both are normally open The blood which enters the right side of the heart has ample opportunity to pass to the left side The blood in the right auricle can pass directly to the left auricle and also into the right ventricle The blood from the right ventricle is pumped into the pulmonary artery Nevertheless, only a small amount of the blood in the pulmonary artery flows to the lungs, the greater part passes directly through the ductus arteriosus into the descending aorta

The normal fetal circulation shown in Diagram 1–1 may be briefly summarized as follows The blood which enters the right auricle through the superior vena cava flows into the right ventricle and is pumped out into the pulmonary artery Inasmuch as the fetal lungs are collapsed only a small amount of the blood in the pulmonary artery flows through the two main branches of the pulmonary artery to the lungs most of the blood in the pulmonary artery flows through the ductus arteriosus to the descending aorta Some of the blood is returned by the inferior vena cava to the right auricle the remainder of the blood flows through the hypogastric artery to the umbilical arteries and thence to the placenta where the waste products are given off and oxygen is taken up The blood from the placenta is returned by the umbilical veins to the liver then through the ductus venosus to the inferior vena cava and thence to the right auricle Most of the blood from the inferior vena cava is directed across the right auricle through the foramen ovale to the left auricle where it meets the small volume of blood which is returned from the lungs by the pulmonary veins The blood from the left auricle flows into the left ventricle, is pumped out through the aorta to the head and the upper extremities, and flows through the descending aorta to the trunk and the lower extremities The blood from the head and

Diagram 1–1

Normal fetal circulation

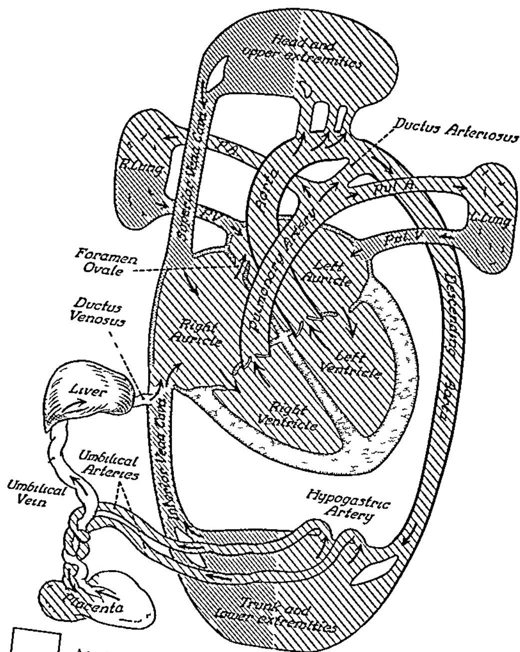
During fetal life the lungs do not function The fetus receives oxygenated blood from the placenta by way of the umbilical veins The umbilical veins pass through the liver and join the inferior vena cava by way of the ductus venosus Thus the inferior vena cava as it enters the right auricle contains a mixture of oxygenated blood from the placenta and venous blood from the fetus

Most of the blood from the inferior vena cava is directed across the right auricle through the foramen ovale to the left auricle Here it meets the venous blood which is returned from the lungs this combination of partially oxygenated and venous blood passes from the left auricle to the left ventricle and out by way of the aorta to the head and upper extremities and some blood also flows through the descending aorta to the trunk and lower extremities

The blood from the head and upper extremities is returned by way of the superior vena cava to the right auricle The greater part of the blood from the superior vena cava is directed to the right ventricle The blood in the right ventricle is pumped out into the pulmonary artery Part of the blood in the pulmonary artery passes through the main branches of the pulmonary artery to the lungs through which it circulates but from which it receives no oxygen and is returned by way of the pulmonary veins to the left auricle Most of the blood from the pulmonary artery passes through the ductus arteriosus to the aorta thence the blood flows through the descending aorta to the trunk and lower extremities Here again the stream divides part of the blood is returned to the right auricle by way of the inferior vena cava and part flows through the hypogastric arteries to the umbilical arteries and out to the placenta for oxygenation

During fetal life the work of the right ventricle is increased because the right ventricle *not only pumps the blood against the high pressure of the collapsed lungs but* also pumps blood through the ductus arteriosus to the trunk and lower extremities In contrast to this the left ventricle pumps the blood to the head and upper extremities and only part of the blood to the trunk and lower extremities Hence during intrauterine life the left ventricle does less work and the right ventricle does more work than after birth Consequently at birth the wall of the right ventricle is of approximately the same thickness as that of the left ventricle Although the electrocardiogram at birth and during the neonatal period normally shows a right axis deviation the unipolar leads indicate that the two ventricles are of approximately equal thickness

DIAGRAM I-I



Arterial blood (fully saturated)

Small admixture of venous blood
No visible cyanosis

Venous and arterial blood
Cyanosis visible

Venous blood

the upper extremities is returned by the superior vena cava to the right auricle and thence to the right ventricle The blood which is directed to the trunk and lower extremities meets the blood which is pumped from the right ventricle through the ductus arteriosus into the descending aorta Part of the blood in the descending aorta flows to the placenta, and part is returned by the inferior vena cava to the right auricle

There are two points in the fetal circulation which are controversial first, the extent of the separation of the blood into two streams in the right auricle, and second, the extent to which the fetus breathes in utero The work of Barclay, Franklin, Prichard, and their associates [4, 5] indicates that in a number of the lower animals there is an almost complete separation of the two streams In some species the foramen ovale is not merely a valve but a tube which directs the stream of blood from the inferior vena cava into the left auricle, whereas the blood from the superior vena cava is directed into the right ventricle Consequently in these animals the oxygen content of the blood in the left ventricle is higher than that in the right How closely the anatomical structure and the functional capacity of the human fetal heart resemble those of the lower animals is not known Nor is it known to what extent the lungs expand during intra uterine life Certain it is that the lungs do not serve for the oxygenation of the blood The blood which goes to the lungs is returned unoxygenated by the pulmonary veins to the left auricle The partially oxygenated blood from the inferior vena cava which is directed into the left auricle mixes with the venous blood which is returned from the lungs Therefore, it seems probable that there is no significant difference in the oxygen content of the blood in the left and the right side of the fetal heart The supply of oxygen to the fetus from the mother s blood is extremely meager, it is, however adequate for the normal growth and development of the fetus

Furthermore both sides of the heart pump the blood through the body of the fetus The left ventricle pumps the blood into the aorta and hence pumps against the systemic pressure Inasmuch as the lungs are collapsed and the blood which cannot pass to the lungs is pumped through the ductus arteriosus to the descending aorta the right ventricle also works against systemic pressure Thus the work required of the two ventricles is approximately the same Consequently at birth the walls of the two ventricles are of approximately the same thickness The wall of the left ventricle is proportionately not as thick as in adult life and that of the right ventricle is proportionately thicker These changes are reflected in the electrocardiogram Although during the neonatal period it is normal for

the electrocardiogram to show a right axis deviation, the precordial leads indicate that the two ventricles are of approximately equal thickness

The fact that the lungs are of no functional importance during intra uterine life means that many of the malformations which affect the right side of the heart place no strain on the fetal circulation Such malformations are readily compatible with fetal life For example not until birth and the establishment of respiration does a pulmonary atresia place a serious strain on the circulation Consequently a fetus with such a malformation usually lives to term hence, such malformations are relatively common in newborn babies

CHANGES IN CIRCULATION AT BIRTH

The fact that a malformation places no strain on the fetal circulation does not mean that the same will be true after birth In order for an infant to live until term it is necessary only that the structure of the heart be such as to meet the needs of the fetal circulation, that is the heart must be able to pump the blood around the body of the fetus

At birth a fundamental change in the circulation occurs Not only does the heart pump the blood throughout the body but a mechanism must immediately be set in motion for the exchange of oxygen and carbon dioxide in the lungs Instead of one circulation two circulations are established the systemic circulation which carries oxygenated blood to the body and the pulmonary circulation which enables the blood to give off carbon dioxide and take up oxygen

With the expansion of the lungs and the consequent fall in the pulmonary pressure the blood in the pulmonary artery is directed to the lungs An increased volume of blood is returned to the left auricle, which raises the pressure in that auricle With the rise of the pressure in the left auricle, the valve covering the foramen ovale tends to close Whether this is the mechanism by which the closure of the foramen ovale is accomplished or whether there is something inherent in the structure of the left auricle is not known The work of Barclay Franklin and Prichard [4] indicates that the contraction of the left auricle in itself tends to close the foramen ovale The equalization of the pressures in the two auricles acts to keep it closed during diastole

Be that as it may, with the establishment of respiration, the pressure in the pulmonary circulation becomes less than that in the systemic circulation Consequently the direction of the flow of blood through the ductus arteriosus is reversed Soon the pressures on the two sides of the heart become approximately equal Thereupon the flow of blood through the ductus arteriosus virtually

ceases All the present experimental evidence indicates that although anatomical closure of the ductus arteriosus may not be completed for two months, functional closure of the ductus arteriosus occurs shortly after birth

EVALUATIONS OF THE STRUCTURE OF THE HEART FOUND AT AUTOPSY

Anatomical patency of the foramen ovale and the ductus arteriosus are normal in the neonatal period Failure to appreciate the normality of these findings in the first weeks of life has led to a widespread misconception that in an infant dying of a congenital malformation of the heart the diagnosis of a patent ductus arteriosus or a patent foramen ovale is the one most likely to be substantiated at autopsy Although it is anatomically a correct diagnosis, the condition *per se is seldom fatal in early infancy Moreover, the diagnosis of a patent ductus* arteriosus is likely to give false hopes to the parents or discredit to the physician, since it is widely known that the disturbance in the circulation caused by the persistent patency of the ductus arteriosus can be corrected by surgery As a matter of fact, in most infants who show persistent cyanosis and die at an early age, the patency of the ductus arteriosus aids in the circulation of the blood to the lungs Under such circumstances, ligation of the ductus would be a fatal mistake The conditions under which patency of the ductus arteriosus or of the foramen ovale should be considered as malformations are discussed in detail in their respective chapters in Volume II

It is also important to remember that the structure of the heart found at autopsy does not necessarily represent the structure of the heart throughout the infant s life In a number of malformations the patency of the ductus arteriosus or of the foramen ovale is essential for the maintenance of the circulation As one or both of these structures undergoes normal obliteration, the condition may become so extreme as to render the malformation incompatible with life, and death ensues

SUMMARY

Malformations of the heart follow specific patterns There are however all grades of severity of almost all malformations

Embryological studies indicate that malformations are the result of developmental errors—arrest or defective development at some specific point

Virtually the entire development of the heart occurs between the twenty first and the fortieth day of fetal life Hence this is the time when malformations occur

The salient features in the embryology of the heart are reviewed

The relation of malformations of the heart to embryological defects is presented

Although the etiology is not clear both intrinsic factors and heredity play a role The occurrence of the various syndromes indicates that injury may be both specific and widespread Extrinsic factors also affect the embryo Thus developmental errors may be due to defective genes or to abnormalities in the environment German measles during early pregnancy is associated with a high incidence of congenital cataracts and congenital malformations of the heart

Inasmuch as malformations of the heart result from localized arrest in the development of the heart the remainder of the heart develops as nearly as possible in the normal manner It follows that in most instances the malformed heart occupies the normal position This renders it possible to analyze which chambers are enlarged which absent By this means it is often possible to make a relatively accurate clinical diagnosis as to the nature of the malformation

The age at which the heart assumes its characteristic shape varies with the nature and the severity of the malformation The size and shape of the heart at birth depend upon the strain placed on the abnormal heart during fetal life The ultimate size and shape of the heart depend upon the duration of life and the strain placed upon the abnormal heart by the extra uterine circulation Fortunately many malformations place a constant load upon the heart In such instances once the heart has adjusted to its load the further increase in the size of the heart is proportional to the growth of the individual

A brief review of the fetal circulation and of the changes which take place at birth is given

In the evaluation of the nature of the malformation found at autopsy it is important to bear in mind that the ductus arteriosus and the foramen ovale are normally patent during the neonatal period Moreover the extreme condition *found at autopsy does not necessarily represent the condition present throughout* life When the circulation becomes incompatible with life the infant dies

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CHAPTER II

METHODS OF DIAGNOSIS

THE possibility of a congenital malformation of the heart is suggested by the detection of an unusual murmur or thrill, by the occurrence of cyanosis with or without clubbing of the extremities, or by an abnormality in the size, shape, or position of the heart Any of these findings may suffice to make a positive diagnosis of a cardiac abnormality Detailed study is, however, usually necessary to determine the nature of the malformation A large number of malformations can be differentiated by careful analysis of the information obtained from the history, physical examination, x ray or fluoroscopic studies, and electrocardiography In some instances additional studies, such as the determination of the oxygen saturation of the arterial blood, the circulation time, cardiac catheterization angiocardiography or aortography are necessary for accurate diagnosis These are discussed in Chapter III and the physiological factors are analyzed in Chapter IV This chapter is concerned with basic information derived from physical examination x ray fluoroscopy, and electrocardiography

Physical Examination

The normal physical findings in adults are familiar to all The following discussion is concerned primarily with the variations which occur in infants and young children

An infant s heart is larger in proportion to the chest than is that of an adult Nevertheless accurate percussion of the cardiac borders is difficult Furthermore the actual size of the heart is extremely small The length from base to apex may be only 4 cm Thus an error of one centimeter in percussion is relatively great Moreover, the small size of the heart makes it virtually impossible to differentiate between a basal systolic murmur and one that originates beneath the sternum in the third or fourth interspace In addition the chest wall is so thin that the heart sounds and murmurs are widely transmitted The consequence is that although in older individuals the character of the murmur its location and its transmission are of great significance in infants the heart is so small and the wall of the chest so thin that these findings have little diagnostic importance Furthermore murmurs associated with congenital malformations of the heart depend upon the relative pressure in the two circulations In infancy the differ

ence in pressure is slight, with variations in the systemic and pulmonary pressures murmurs come and go Therefore, too great emphasis should not be placed on murmurs

A murmur which is audible in the neonatal period may or may not be of significance It is a well known fact that a loud systolic murmur may be heard shortly after birth and subsequently disappear Such murmurs are believed to be associated with the flow of blood through the ductus arteriosus Immediately after birth, as the lungs expand there is an abrupt lowering of the pulmonary pressure, indeed normally the pressure in the pulmonary circulation may become sufficiently low to allow the blood to flow from the aorta through the ductus arteriosus to the lungs With the full expansion of the lungs and the establishment of the pulmonary circulation the pressure in the pulmonary artery tends to rise, and the difference between the pressures in the pulmonary and systemic circulations becomes relatively slight Normally the ductus arteriosus undergoes obliteration but even while it remains patent during the ensuing weeks the pressures in the two circulations become so nearly equal that the murmur usually disappears Functional closure of the ductus arteriosus occurs long before anatomical closure of this pathway

The persistence of a murmur for a period of weeks is usually indicative of a congenital malformation of the heart Most of these murmurs are *systolic* in time Because of the small size of the heart it is virtually impossible, with the single exception of a dextrocardia, to localize a murmur with sufficient accuracy for it to be of diagnostic significance Furthermore the intensity of the murmur although affected by the size of the opening depends primarily upon the relative pressure in the greater and the lesser circulations When the pressures in the two circulations become equal the murmur disappears Therefore only rarely is the location of the mumur or its intensity of diagnostic aid

Diastolic murmurs are of significance but such murmurs are comparatively rare in infants under a year of age In infancy an early diastolic murmur maximal along the left sternal border is more frequently due to pulmonary insufficiency than to aortic insufficiency True presystolic murmurs are very seldom heard because congenital mitral stenosis is rare Furthermore, when mitral stenosis is extremely severe there may be no murmur

Continuous murmurs are of significance Although such a murmur is always suggestive of persistent patency of the ductus arteriosus in early infancy a continuous murmur is quite as frequently heard in a truncus arteriosus or an aortic septal defect as in a patent ductus arteriosus Furthermore, such a murmur may

be produced by a congenital anomaly of the pulmonary orifice The author has seen one infant who had a loud, ringing diastolic murmur which was continuous with a systolic murmur over the pulmonary area Autopsy revealed a malformation of both the aortic and the pulmonary valves The cusps of the aortic valve were of unequal size, and one cusp was placed at a lower level than the other two, thus the aortic valve appeared to be insufficient The pulmonary orifice was diminutive in size, and the pulmonary valves entirely absent Consequently, although great difficulty was encountered in the expulsion of blood through the pulmonary orifice during diastole there was nothing to prevent the free regurgitation of blood into the right ventricle The continuous murmur was readily accounted for by the pulmonary stenosis combined with pulmonary insufficiency, and possibly by the aortic insufficiency No remnant of the ductus arteriosus was found

Breath sounds in infants are frequently confused with heart sounds This may lead to the mistaken diagnosis of a continuous murmur At the apex it is important to differentiate between a true diastolic murmur and the gallop rhythm of a poorly functioning heart Because diastolic murmurs are rare and subject to misinterpretation and because many of the systolic murmurs are extremely variable and impossible to localize with accuracy, the main importance of a murmur is to direct attention to the possibility of a malformation Further studies are necessary in order to ascertain the nature of the malformation

In infancy the features which are of diagnostic significance are the rate and the action of the heart and the quality of the heart sounds A loud murmur, especially if accompanied by a thrill or by the occurrence of cyanosis is always of significance

The heart rate should be counted A slow, regular heart rate (30 to 50 per minute in an adult 60 per minute in a child, and 80 per minute in an infant) should suggest the possibility of a complete heart block Excessively rapid rates occur with cardiac failure Cardiac arrhythmia auricular fibrillation paroxysmal tachycardia and even excessive sinus tachycardia are prone to occur when one or both auricles are enormously dilated (see Chapters v and xxxv)

The forcefulness of the heart sounds is often of diagnostic significance Although in early infancy the heart sounds are normally relatively loud extremely loud heart sounds may be the only indication that the heart is laboring under great difficulties The forcefulness of the heart action may thus arouse suspicion before the development of a murmur or the recognition of cardiac enlargement

The quality of the second sound at the base also gives useful information The

reduplication of the second sound is clear evidence of the existence of both great vessels It is never heard when there is atresia of one of the great vessels or a truncus arteriosus The converse is not uniformly true the absence of reduplication of the second sound is not positive proof that there is but one great vessel However, the purity of the second sound in cases of atresia of one of the great vessels is striking

Accentuation of the second sound over the pulmonary area usually means that the right ventricle is working against an abnormally high pulmonary pressure It is however, important to remember that the accentuation of the second sound may be due to an abnormal rotation of the great vessels such that the closure of the aortic valve is better heard to the left of the sternum than to the right

A murmur always directs attention to the heart Even in infancy, functional murmurs must be differentiated from those caused by a congenital malformation of the heart In young children it is also important to differentiate murmurs due to congenital malformation from those due to acquired heart disease

Functional murmurs are common They are sometimes difficult to differentiate from murmurs produced by congenital malformations If however, the presence of a murmur is the only abnormality if the heart is of normal size and shape, and if its functional capacity is good the existent malformation if present, is probably slight. If, however, there is any doubt the baby should be kept under close observation Nevertheless so long as the baby is doing well and the heart remains normal in size no further studies are necessary

Murmurs of acquired heart disease follow the pattern of valvular lesions The murmur of mitral insufficiency is well transmitted to the axilla that of mitral stenosis is localized just within the apex and is heard best in the left lateral position after exercise The early diastolic murmur of aortic insufficiency is heard along the left sternal border and that of aortic stenosis is maximal at the base of the heart to the right of the sternum and is transmitted to the great vessels A systolic murmur over the pulmonary area or along the left sternal border if intense is always suggestive of a congenital malformation of the heart

In infants most murmurs which are clearly indicative of a malformation of the heart are loud rasping systolic murmurs which have the quality commonly thought characteristic of a small ventricular septal defect of the maladie de Roger type This malformation is, in reality by no means as common as might be expected from the frequency of loud precordial systolic murmurs

The presence of a pronounced thrill is almost always indicative of the exist

ence of a cardiac abnormality Care should be taken to palpate over the entire precordium The mistake is often made, especially in the examination of older individuals, of palpating at the apex only and neglecting to palpate along the sternum and over the base of the heart The time of the thrill is important Most thrills are systolic in time A continuous thrill over the base of the heart is suggestive of a patent ductus arteriosus Broadly speaking thrills are indicative of loud murmurs and of a considerable disturbance in the flow of blood For this reason a murmur often becomes audible before the development of a palpable thrill Indeed, it is unusual to feel a thrill in a baby less than four months of age

Left sided chest deformity is always indicative of great right sided cardiac enlargement It is only when the right ventricle is so greatly enlarged that it presses against the anterior chest wall that the heart causes deformity of the chest Furthermore such pressure must occur while the bones are soft and pliable therefore, left sided chest deformity is always indicative of right sided cardiac enlargement which has occurred at a relatively early age This, however, does not mean that the enlargement is due to a congenital malformation of the heart it may be the result of a severe rheumatic infection

The rate of growth and the degree of development of the individual may offer a clue to the severity of the cardiac anomaly Prolonged severe anoxemia frequently causes stunting of growth In addition stunting of growth may be due to a huge left to right shunt of such magnitude that the body lacks an adequate supply of oxygenated blood as for example in a patient with a large patent ductus arteriosus or with a large septal defect

*Cyanosis and clubbing** are always suggestive of a severe malformation of the heart Cyanosis always precedes clubbing of the extremities Indeed clubbing of the extremities although a characteristic finding in older patients, is seldom seen in early infancy In infancy, in the vast majority of instances, persistent cyanosis indicates not only that there is some abnormal communication between the two sides of the heart, but also that a large volume of venous blood is being pumped directly into the systemic circulation The commonest causes of such shunts are malformations of the great vessels and the manner in which they meet the ventricles

The intensity of the cyanosis especially in relation to the concentration of the hemoglobin, should be considered Slight cyanosis with a hemoglobin level of 10 gm may be far more serious than deep cyanosis with a hemoglobin level of 17 gm

The distribution of the cyanosis should be studied with care A difference,

* The factors which produce cyanosis are discussed in detail in Chapter II

even though not always pronounced, in the intensity of the cyanosis of the upper and lower extremities gives valuable information concerning the course of the circulation When the feet are more cyanotic than the hands, venous blood is flowing from the pulmonary artery through the ductus arteriosus into the descending aorta When there is a complete interruption of the isthmus of the aorta and the descending aorta is continuous with the pulmonary artery through the ductus arteriosus, the difference in cyanosis between the upper and the lower extremities is marked because the lower extremities receive only venous blood from the pulmonary artery The reverse distribution of cyanosis may occur in association with a complete transposition of the great vessels (see Chapter x)

In patients with pulmonary hypertension and patency of the ductus arteriosus (see Chapter xviii), the pressure in the lesser circulation may be so high that some of the venous blood which flows from the pulmonary artery into the aorta is forced back into the left subclavian artery, thus, the left hand becomes more cyanotic than the right Occasionally the right hand is of normal color, the left hand slightly cyanotic and the feet definitely cyanotic In most instances the difference in cyanosis is slight but becomes readily apparent when the right hand is placed beside the foot

The strength of the pulse especially that in the arm compared with that in the leg is significant A strong pulse in the upper extremities combined with a weak or absent pulse in the lower extremities is characteristic of coarctation of the aorta In contrast to this, in an infant with aortic atresia the pulse everywhere may be so weak that it is difficult to palpate With cardiac failure also the pulse may be extremely weak

Cardiac failure is indicated by a gallop rhythm, by the rapidity of the respirations by the enlargement of the liver by rales in the lungs and by edema of the extremities (see Chapter v)

Gallop rhythm is indicative of a poorly functioning heart It is commonly heard when the heart is greatly enlarged in a heart of normal size it is indicative of a poorly functioning heart

The respiratory rate in infancy and childhood is the most sensitive index of cardiac decompensation Although infants breathe more rapidly than adults, extremely rapid respirations are always suggestive of cardiac failure Many infants breathe quietly therefore, the rapidity of the respiratory rate is frequently not appreciated unless it is counted A respiratory rate of 60 per minute is a sign of distress If the respirations are grunting in character, they call for differentiation from those associated with pneumonia

Rales in the lungs result from pulmonary congestion In order to have pulmo-

nary congestion, there must be adequate circulation to the lungs Many malformations, notably most of those which cause persistent cyanosis, are associated with a marked diminution in the flow of blood to the lungs For this reason, pulmonary congestion and the rales at the bases of the lungs are extremely rare in patients with pulmonary stenosis or atresia The converse is also true in the presence of cyanosis rales in the lungs are suggestive of a malformation in which there is adequate or excessive pulmonary blood flow For example, rales in the lungs are relatively common in patients with complete transposition of the great vessels Pulmonary congestion also occurs in patients with large left to right shunts

Engorgement of the liver is the usual early sign of cardiac failure in infancy and childhood It is indicative of a right sided heart failure and occurs long before there are rales in the lungs or demonstrable edema of the extremities

Pulsations at the margin of the liver when they occur, are of diagnostic aid They are indicative of an abnormality of the tricuspid valve—either of tricuspid insufficiency or of tricuspid stenosis or atresia with a well formed auricular septum In patients with tricuspid insufficiency the pulsations at the margin of the liver are systolic in time, whereas in patients with tricuspid stenosis or atresia they are presystolic in time Furthermore in tricuspid insufficiency the right ventricle is enlarged, whereas in tricuspid stenosis or atresia the right ventricle is small or absent Tricuspid insufficiency is usually associated with engorgement of the liver When the liver is of normal size, pulsations at its margin are strongly suggestive of tricuspid stenosis or atresia with a well formed auricular septum in which there is only a small opening between the two auricles (see Chapter VIII)

In summary physical examination usually reveals a cardiac abnormality The detection of a murmur always arouses suspicion The occurrence of chest deformity, the abnormal location of the apex beat, or the presence of cyanosis and clubbing immediately suggests the existence of some congenital malformation of the heart Accurate diagnosis of the nature of the malformation, especially in infants and young children, is seldom possible without the aid of the fluoroscope and the electrocardiogram

Fluoroscopic and X Ray Examinations

Fluoroscopic and x ray examinations in the anterior posterior position demonstrate the size of the heart and the great vessels and in the oblique positions it is possible to determine which chambers and vessels are enlarged and which

are absent Such changes are of prime importance in the diagnosis of the major ity of the severe malformations of the heart

Fluoroscopic examination is generally more valuable than x ray examina tion because it permits the examination of the patient in a number of positions and also because artifacts produced by the rotation of the head and shoulders, and variations in the size of the heart produced by respiration or crying can be eliminated In addition, it is possible to detect pulsations in the lung fields and any actual changes in the shape of the heart which may occur in the various phases of the cardiac cycle

Although fluoroscopy is of greater aid in diagnosis than is x ray it must be remembered that the patient receives far more radiation from a fluoroscopic ex amination than from an x ray Image intensifiers greatly reduce the danger of radiation, but without such protection repeated fluoroscopy is contraindicated

CONTOUR OF THE NORMAL HEART

In order to evaluate the changes in the x ray shadows produced by the mal formed heart, it is essential to understand the contour of the normal heart * The main differences between the adult and the infant are that in the infant the chest is rounder, the diaphragm is higher, and the heart lies in a more horizontal posi tion than in the adult Indeed, in the infant the chest is wider than it is long in the child approximately as long as it is wide and in the adult longer than it is wide In the anterior posterior position† the right ventricle always lies anterior to the left ventricle Thus, the left border of the cardiac shadow is composed of the pulmonary conus the margin of the right ventricle and the apex of the left ventricle The term pulmonary conus is used to denote the second curve to the left of the sternum which lies at the base of the heart normally it is composed of the main pulmonary artery and the outflow tract of the right ventricle It is however, frequently impossible to determine exactly where one ends and the other begins The studies of Robb and Steinberg[7] demonstrate that normally in adults the tip of the left auricle is not visible in the anterior posterior position certainly it is not visible in infants and children The right auricle is seen to the right of the sternum Above the right auricle the superior vena cava may project

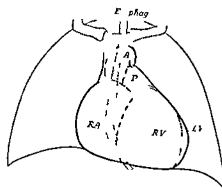
The discussion of the contour of the normal adult heart is based on the work of Evans[1] Palmer Bedford and Parkinson[3] Assmann[4] and Roesler [6] and on studies of various models and autopsy materials The discussion of the contours of the hearts of infants and children is based on the observations of the author

†The term anterior posterior is used throughout the book to describe the patient s posi tion when he is facing the screen

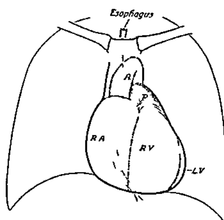
slightly to the right of the sternum In adults the aortic knob is normally seen to the left of the sternum, in infants it is normally not visible The contours of the heart and chest of the normal infant, child, and adult in the anterior posterior position are shown in Figure 11–1, the anterior posterior position relative to the fluoroscopic screen is shown in the upper drawing of Figure 11–2

In the left anterior oblique position the patient is placed so that his left shoulder is toward the screen and he is facing the left shoulder of the observer (as shown in the middle drawing of Figure 11–2) The patient is rotated so that his shoulder meets the screen at an angle of 45° This position makes it possible to differentiate between the right ventricle and the left In this position the two ventricles lie side by side and the apex points toward the observer, the right ventricle projects toward the anterior chest wall, and the left ventricle extends toward the spinal column Therefore, the right border of the cardiac silhouette, that is, that portion which projects toward the anterior chest wall, is formed by the right ventricle The left margin of the cardiac shadow, that portion which projects posteriorly toward the spinal column, is cast by the left ventricle Thus, each ventricle contributes its specific component to the cardiac silhouette On deep inspiration it may be possible to visualize the interventricular groove and thereby accurately identify the portion of the cardiac silhouette contributed by each of the ventricles This position also gives the best visualization of the ascending aorta and the aortic arch The pulmonary artery lies anterior to the ascending aorta and although not clearly visualized adds a component to this shadow The pulmonary window is also visualized in this position, it lies posterior to the main pulmonary artery, immediately below the arch of the aorta The pulmonary window includes the aortic window and the region normally occupied by the pulmonary artery The left auricle constitutes part of the posterior shadow at the base of the heart and its upper margin forms the lower boundary of the pulmonary window but the left auricle is not sufficiently clearly delineated to be of diagnostic significance The right auricle normally is not visible, it lies almost directly behind the right ventricle Figure 11–2 shows the position of the child relative to the fluoroscopic screen and the contour of the heart in each of the three positions

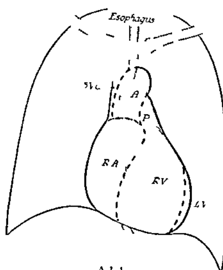
In the right anterior oblique position the patient is rotated so that his right shoulder is toward the screen and he faces the right shoulder of the observer (as shown in the bottom drawing of Figure 11–2) In this position the major part of the cardiac shadow is cast by the right auricle and the right ventricle The right auricle forms the posterior part of the cardiac shadow and lies just in front of the spinal column and projects forward toward the observer The anterior portion



Infant



Child



Adult

FIGURE II-1 Normal heart

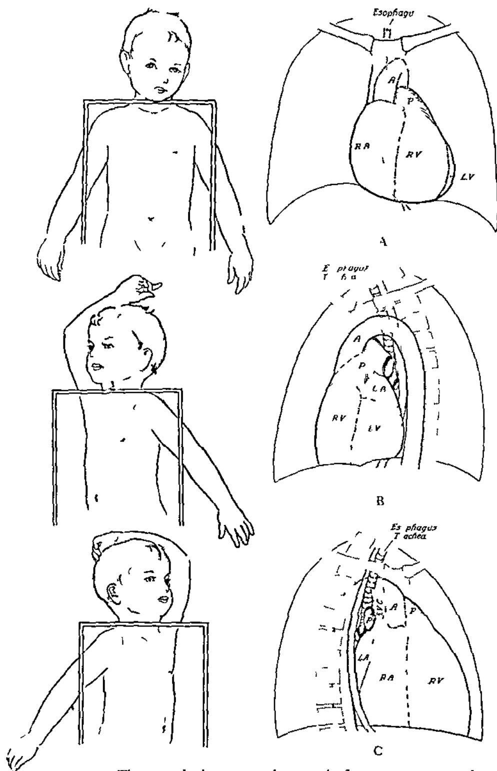


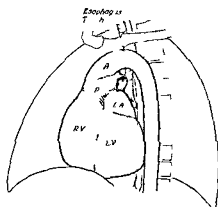
Figure II– Three standard positions relative to the fluoroscopic screen and contour of the normal heart in each position Child
(A) Anterior posterior (B) left anterior-oblique (C) right anterior-oblique

of the cardiac shadow, that is, the portion which lies close to the anterior chest wall, is composed of the right ventricle In this position the right auricle and the right ventricle completely obscure the left ventricle The shadow at the base of the heart is composed of the pulmonary conus, that is, the outflow tract of the right ventricle and the main pulmonary artery Immediately below and posterior to this shadow, the portion of the cardiac silhouette which lies close to the spinal column is a composite shadow cast by the aorta the bifurcation of the trachea, the pulmonary arteries, the esophagus, and the left auricle The differentiation of the various components of this shadow is difficult Nevertheless when the esophagus is filled with an opaque mixture * it is possible to visualize its position relative to the course of the aorta and the left auricle Normally the aorta as it arches posteriorly may slightly indent the esophagus The left auricle lies adjacent to the esophagus and may pulsate against it, but does not alter the course of the esophagus Enlargement of the left auricle causes backward displacement of the esophagus (see Figures 11–7 11–9 11–10 and page 47)

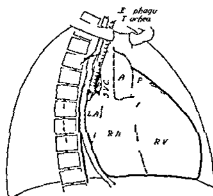
The above review of the contour of the heart shows that by examination in the anterior posterior and the two oblique positions all four chambers of the heart can be visualized The anterior posterior position gives the size of the two ventricles and the right auricle The examination in the left anterior-oblique position shows the relative size of the right and the left ventricles In the right anterior-oblique position it is possible to visualize the size of the left auricle The contour of the normal heart of the infant and adult in the left and right anterior oblique positions is shown in Figure 11–3 By studies in these three positions it is possible to differentiate the changes in the contour of the heart which result from the enlargement or absence of each of the various chambers

It is also important to bear in mind the changes in the contour of the heart which occur with growth As the infant grows to childhood the diaphragm drops down and the heart occupies a more vertical position This means not only that the apex lies at a lower level and that the heart is smaller in proportion to the chest but also that the great vessels become elongated The pulmonary conus is less conspicuous and the shadow cast by the great vessels is narrower Furthermore as the individual grows the aortic knob becomes more readily visible These changes are shown in Figure 11–1

* A small quantity of barium should be mixed with an approximately equal amount of water this should be sweetened and flavored to make a palatable mixture Three teaspoonfuls of barium sulphate three teaspoonfuls of water and one teaspoonful of sweetened cocoa is a mixture which most children enjoy

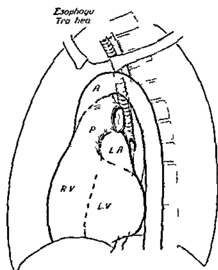


Left anterior-oblique position

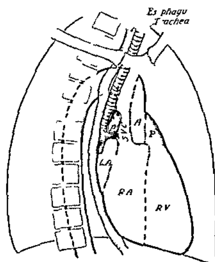


Right anterior-oblique position

INFANT



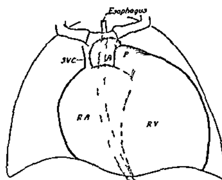
Left anterior oblique position



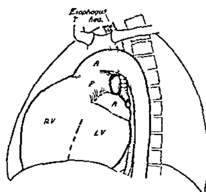
Right anterior-oblique position

ADULT

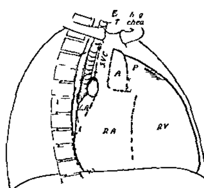
FIGURE 11-3 Normal heart Infant and adult



Anterior posterior position



Left anterior-oblique position



Right anterior-oblique position

FIGURE II-4 Great enlargement of the right auricle and the right ventricle Infant

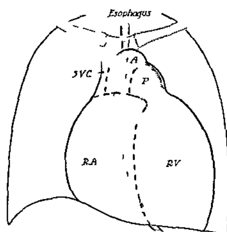
ENLARGEMENT OF THE RIGHT VENTRICLE

The right ventricle is well outlined in both the anterior posterior and the left anterior-oblique positions In the anterior posterior position enlargement of the pulmonary artery and of the outflow of the right ventricle is indicated by an accentuation of the shadow cast by the pulmonary conus (Figure II-4) Since the remainder of the right ventricle lies anterior to the left ventricle, the anterior posterior position shows the size of the heart and enlargement of the ventricles when present, but gives no evidence whether it is the right or the left ventricle which is enlarged Examination in the left anterior oblique position permits the differentiation between right and left ventricular enlargement In this position, as previously mentioned, the right ventricle projects toward the anterior chest wall the left ventricle toward the spinal column (see Figure II-4) The relation

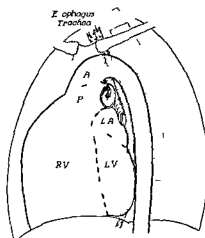
of the right ventricle to the aorta is a useful guide in the estimation of the size of that chamber With marked enlargement of the right ventricle, the shadow cast by that ventricle projects further and further forward beyond the ascending aorta until with tremendous enlargement, the right ventricle presses against the anterior chest wall When progressive enlargement of the right ventricle occurs early in life, it will sooner or later push the anterior chest wall forward As previously stated, left sided chest deformity usually means right sided cardiac enlargement If the enlargement of the right ventricle occurs after the chest wall has lost its flexibility, the right ventricle becomes flattened against it, and with further enlargement the left ventricle is displaced backward When this occurs, the anterior margin of the cardiac silhouette has a straight border, and the ventricular groove can usually be seen to lie abnormally far posteriorly This phenomenon is most frequently seen when the enlargement of the right ventricle is due mainly to progressive hypertrophy such as occurs in a valvular pulmonary stenosis with an intact ventricular septum (see Figure II–5)

ABSENCE OF THE RIGHT VENTRICLE

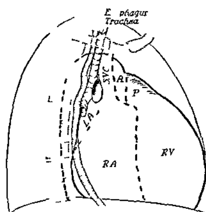
Absence of the right ventricle also causes a distinctive change in the cardiac silhouette (see Chapters VIII and IX) In the anterior posterior position the significant feature is the absence of the shadow cast by the pulmonary conus The absence of this portion of the heart causes the upper margin of the cardiac shadow to the left of the sternum to change from the normal convexity to a concavity, as shown in Figure II–6 It is important to remember that the development of the outflow tract of the right ventricle is intimately associated with the development of the normal pulmonary artery Absence of the pulmonary conus occurs whenever the pulmonary artery fails to meet the right ventricle in the normal fashion It indicates that the pulmonary artery is absent, diminutive, or misplaced Thus the absence of the shadow cast by the pulmonary conus may be associated with a pulmonary atresia and a non functioning right ventricle, or with a complete transposition of the great vessels and a greatly enlarged right ventricle It follows that the absence of the pulmonary conus gives no indication of the size of the right ventricle In order to ascertain whether or not the right ventricle is diminutive examination in the left anterior-oblique position is essential When there is a defective development of the right ventricle the cardiac shadow never projects toward the anterior chest wall beyond the margin of the ascending aorta It is, however important to remember that when the right ventricle is absent, the left ventricle is always enlarged Owing to the enlargement of the



Anterior posterior position



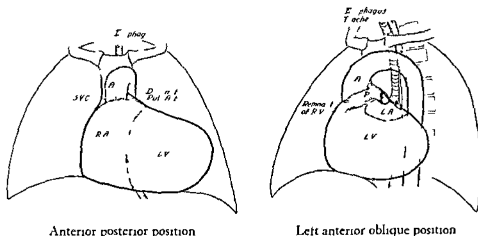
Left anterior oblique position



Right anterior-oblique position

FIGURE II–5 Enlargement of the right auricle right ventricular hypertrophy and poststenotic dilatation of the pulmonary artery Child

Note the flattening of the anterior margin of the right ventricle against the anterior chest wall and the interventricular groove in the left anterior-oblique position



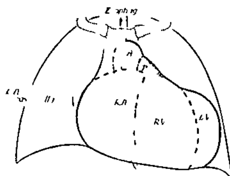
Anterior posterior position — Left anterior oblique position

FIGURE II–6 Absence of the right ventricle Infant

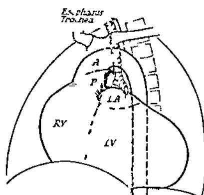
left ventricle the cardiac silhouette is not smaller than normal, but the contour is changed The enlargement extends posteriorly The anterior portion of the cardiac shadow does not project toward the anterior chest wall beyond the margin of the aorta (see Figure II–6 and Chapter VIII)

ENLARGEMENT OF THE LEFT VENTRICLE

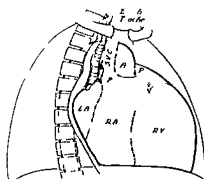
The left ventricle as well as the right is visualized in both the anterior posterior and the left anterior oblique positions The basic contour of the left ventricle is seen in cases in which the right ventricle is absent (see Figure II–6) In the normal heart, in the anterior posterior position, it is the lower left margin of the cardiac shadow which is cast by the left ventricle As the left ventricle enlarges when the heart occupies a transverse position in the thorax the cardiac shadow extends further and further outward If the diaphragm is depressed the pulmonary conus becomes inconspicuous but as the outer margin of the heart approaches the lateral chest wall, the apex has a round contour and is slightly upturned (see Figure II–7) The principal enlargement of the left ventricle takes place posteriorly and therefore can be best demonstrated in the left anterior oblique position In this position the size of this ventricle can be estimated by the amount of rotation necessary for the left ventricle to clear the spinal column With progressive enlargement of the left ventricle, it is necessary to rotate the patient further and further toward the lateral position in order for the heart to clear the spinal column In the normal child, according to Wilson,[8, 9] the angle of clearance is 50° plus 55 or more is considered abnormal Although there



Anterior posterior position



Left anterior oblique position



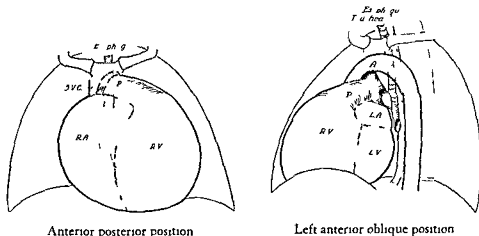
Right anterior-oblique position

FIGURE II-7 Great enlargement of the left auricle and the left ventricle Infant

are no exact figures for infants the method permits a rough but useful means for the estimation of the size of the left ventricle When there is enormous enlargement of the left ventricle, the cardiac shadow is seen to extend posteriorly far beyond the spinal column (see Figure II-7)

DEFECTIVE DEVELOPMENT OR ABSENCE OF THE LEFT VENTRICLE

Absence or defective development of the left ventricle is rare When it does occur, there is always enormous enlargement of the right ventricle Under these circumstances in the anterior posterior position the heart appears enlarged and the pulmonary conus may be abnormally full The small size of the left ventricle is appreciated only in the left anterior-oblique position In this position the right ventricle projects nearly, if not all the way, to the anterior chest wall, in addition the right ventricle projects further posteriorly than normal Thus the right



Anterior posterior position — Left anterior oblique position

FIGURE II-8 Large right ventricle and a small left ventricle Infant

ventricle fills the area normally occupied by the left ventricle Nevertheless there is a striking discrepancy between the sizes of the two ventricles There is enormous enlargement anteriorly, whereas posteriorly the contour of the heart is essentially normal (see Figure II-8 and Chapter XIII)

ENLARGEMENT OF THE RIGHT AURICLE

Enlargement of the right auricle is best seen in the anterior posterior position in this position it extends outward to the right beyond the margin of the sternum In the left anterior-oblique position the right auricle is normally hidden by the right ventricle When the right auricle is greatly enlarged, it may occasionally project above the margin of the outflow tract of the right ventricle and thus cause a sharp anterior bulge at the upper margin of the cardiac silhouette In the right anterior oblique position the right auricle lies posterior to the ventricles Usually it is not specifically outlined in this view At times, however, it is seen to extend posteriorly to the spinal column and occasionally beyond it If the cardiac silhouette extends abnormally far posteriorly the shadow is always caused by enlargement of one or both auricles Delineation of the esophagus with a radio-opaque mixture such as barium permits the differentiation between the two auricles If the shadow is caused by the enlargement of the right auricle, there is no deviation of the esophagus, the esophagus will be seen to lie behind the cardiac shadow (see Figure II-5) If, on the other hand, the left auricle is enlarged there will be backward displacement of the esophagus (see Figures II-7 II-9 and II-10)

ENLARGEMENT OF THE LEFT AURICLE

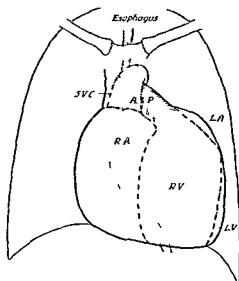
Although in adults with mitral stenosis the tip of the left auricle, when greatly enlarged, is visible in the anterior posterior position to the left of the pulmonary conus, it is rarely seen in children (see Figure 11–9) In infants the left auricle is seldom visible in this position (see Figures 11–7 and 11–10) Even when the pulmonary artery is misplaced and the pulmonary conus is absent and the left auricle is enormously enlarged the tip of the auricular appendage is not visible to the left of the pulmonary artery The left auricle, however, may occasionally be seen to extend to the right of the sternum beyond the margin of the right auricle as indicated in Figures 11–7 and 11–9 Enlargement of the left auricle can always be demonstrated by the delineation of the course of the esophagus with a radio-opaque mixture As the left auricle enlarges it displaces the esophagus backward Although on rare occasions the enlargement of the left auricle is seen in the left anterior-oblique position the backward displacement of the esophagus is usually best seen in the right anterior-oblique position Such displacement if due to a large left auricle is still visible when the patient takes a deep breath (see Figures 11–9 and 11–10)

It is noteworthy that scoliosis seldom, if ever causes displacement of the esophagus Therefore if backward displacement of the esophagus is found in a patient with extreme scoliosis the probability is that the deviation of the esophagus is not due to the scoliosis but is caused by enlargement of the left auricle

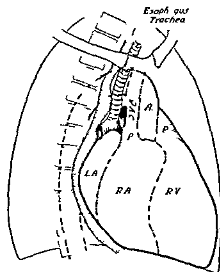
Backward displacement of the esophagus is almost always accompanied by lateral displacement of the esophagus In the right anterior-oblique position such lateral deviation may not be appreciated because it is toward or away from the observer In the anterior posterior position the backward displacement of the esophagus is not apparent but any deviation to the right or left is readily apparent Although the esophagus may be displaced either to the right or to the left (see Figure 11–10) the deviation to the right is more common Inasmuch as backward displacement is visualized in the right anterior oblique position and lateral displacement in the anterior posterior position in order to ascertain the course of the esophagus the patient should always be examined in both positions

STRUCTURE OF THE AURICLES RELATIVE TO THE DEVELOPMENT OF THE AURICULAR SEPTUM

From the functional aspect, abnormalities of the auricular septum may be divided into three groups a patent foramen ovale that is a foramen ovale covered by a valve which is not completely sealed a gross defect in the auricular septum

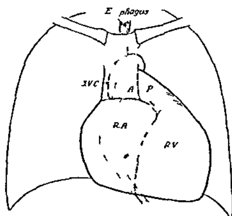


Anterior posterior position

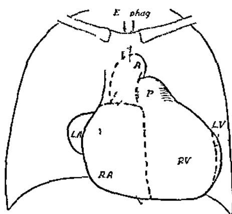


Right anterior-oblique position

ADULT



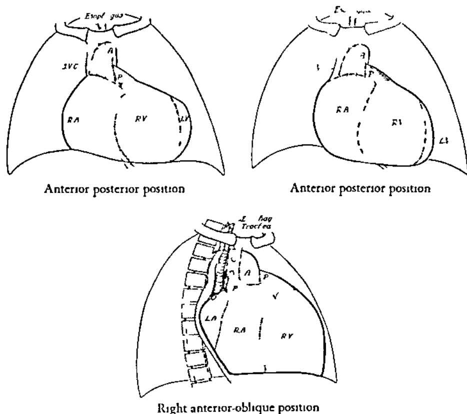
Anterior posterior position



Anterior posterior position

CHILD

FIGURE II-9 Large left auricle Adult and child



Anterior posterior position

Anterior posterior position

Right anterior-oblique position

FIGURE II–10 Large left auricle Infant

Note the variations in the course of the esophagus

with no valve or membrane covering the defect and an absence of the auricular septum or such a rudimentary septum that functionally there is but a single auricle Information concerning the structure of the auricular septum can be deduced from the size of the right auricle and the distention of the superior vena cava, and also from rhythmic changes in the size of the right auricle

A patent foramen ovale guarded by a valve is normally present at birth The normal process for the closure of the foramen ovale is the formation of a membrane on its left side This membrane does not become completely adherent to the wall of the left auricle for many months Indeed an opening through which a probe can be passed remains throughout life in at least 10 per cent of all individuals[10, 11] Therefore, strictly speaking this condition cannot be con-

sidered a malformation It can be correctly described as a foramen ovale which is anatomically patent but functionally closed It is of importance only when the pressure in the right auricle becomes greater than the pressure in the left auricle, under such circumstances, the valve opens and permits the flow of blood from *right to left*

There is a group of malformations of the heart in which this mechanism is important Any abnormality of the right side of the heart sooner or later in creases the work required of the right auricle For example, Ebstein s anomaly of the tricuspid valve causes difficulty in the expulsion of the blood from the right auricle Similarly pulmonary stenosis with an intact ventricular septum and primary pulmonary hypertension increase the work of the right ventricle and then *as the pressure in the right ventricle rises, that in turn increases* the pressure in the right auricle In all three of these conditions, if the foramen ovale is not completely sealed, when the pressure in the right auricle exceeds that in the left auricle, the valve covering the foramen ovale is forced open, and a right to-left shunt is established

In complete transposition of the great vessels, the mechanism of the shunt through the foramen ovale is slightly different because as the pressure in the right auricle rises, that in the left auricle falls Consequently, when the differ ence between the pressures in the two auricles becomes sufficiently great, the valve guarding the foramen ovale is forced open and blood flows from the right auricle to the left, thereupon the pressure in the right auricle falls abruptly and the right auricle collapses simultaneously the pressure in the left auricle rises and the foramen ovale is closed Thereafter the pressure in the right auricle again builds up and the cycle recurs This phenomenon can be observed upon fluoros copy The right auricle can be seen to dilate and collapse and dilate again in rhythmic succession Such rhythmic changes in the size of the right auricle which are independent of the heart rate, strongly suggest that the foramen ovale is covered by a valve which is at times functionally closed and at times function ally open and permits the flow of blood in one direction only, namely from right to left

Gross defects in the auricular septum are discussed in detail in Chapter XXIII Inasmuch as shunt reversal is more frequent in this condition than in ventricular septal defects, any abrupt reversal in the direction of the shunt suggests the pos sibility of an auricular defect

A single auricle is considered to exist when there is no vestige of an auricu lar septum Under such circumstances the two auricles function as a single

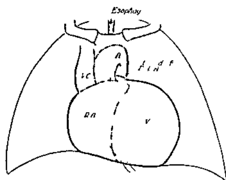


Figure II–11 Dilatation of the superior vena cava absence of the auricular septum and absence of the right ventricle Infant

chamber, but the right side of the auricle appears to bear the brunt of the pressure This is especially true in cases of increased intra auricular pressure, as, for example with atresia or hypoplasia of the mitral or tricuspid valve When there is functionally only a single auricle not only does the right side of the auricle become distended but also the increased pressure impedes the flow in the superior vena cava and it too becomes dilated The engorgement of the superior vena cava causes a conspicuous increase in the width of the shadow to the right of the sternum (see Figure II–11) In early infancy, in the absence of cardiac failure, dilatation of the superior vena cava suggests the existence of a huge defect in the auricular septum

ANALYSIS OF SHADOWS AT THE BASE OF THE HEART

The differentiation of vascular shadows from mediastinal glands should cause no great difficulty Vascular shadows pulsate glands do not The single exception to this statement is the thymus gland

The thymus gland in contrast to mediastinal glands, may show some pulsation at its margin Moreover when enlarged it may widen the shadow at the base of the heart What constitutes a thymus of normal size is controversial The aspect which concerns us here is the differentiation of an enlarged thymus from vascular abnormalities It is not always possible to differentiate the two conditions with certainty indeed occasionally angiocardiography may be necessary to prove that the shadow is not vascular in origin Usually however with marked enlargement of the thymus the shadow at the base of the heart in the anterior posterior position may be widened both to the right and to the left of



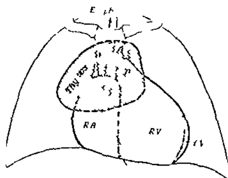


FIGURE 11–12 Thymus Anterior posterior position Infant

the sternum It is more commonly visible to the right of the sternum, as shown in Figure 11–12 Moreover examination in the left anterior-oblique position usually clarifies the situation If the shadow is caused by the thymus, there is almost always a flange visible beyond the aorta, as shown in the diagram of Figure 11–13 Such a wing like projection beyond the aorta is never produced by a vascular abnormality

THE GREAT VESSELS

Normally in infancy the great vessels are concealed behind the sternum Upon rotation of the head to the right, the superior vena cava can be brought into view, upon rotation to the left the aorta and the pulmonary artery become visi



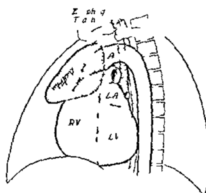


FIGURE 11–13 Thymus Left anterior-oblique po ition Infant

ble to the left of the sternum Thus by turning the head from side to side, it is possible to estimate the size of the great vessels By the same token to obtain a true picture of the heart and great vessels, it is important to have the head in line with the shoulders In older children the aortic knob is visible to the left of the sternum, and in adults the ascending aorta is frequently visible to the right The left lateral position (when the patient is standing at right angles to the screen with the left shoulder toward the screen) gives the best visualization of the aorta as it arches posteriorly and descends upon the left This position is also best for the visualization of the pulmonary artery which is seen to lie directly in front of the aorta

Inasmuch as there are only two great vessels, the number of possible variations is limited There may be enlargement or diminution in the size of, or absence of, either the aorta or the pulmonary artery, there may be a partial or a complete transposition of the great vessels, or there may be a single truncus arteriosus The aorta occasionally descends on the right instead of the left but it always carries blood to the body, the pulmonary artery always leads to the lungs These possible variations may either increase or decrease the width of the shadow cast by the great vessels in one or both positions

ABNORMALITIES OF THE AORTA

Marked enlargement of the aortic knob is usually visible in the anterior posterior position Inasmuch as in infancy the aortic knob is not normally visible, its presence is indicative of marked enlargement of the aorta and immediately suggests the existence of a truncus arteriosus When the transverse arch of the aorta is enlarged, as is usual when the aortic knob is prominent, the arch of the aorta may markedly indent the esophagus This can be visualized in the esophagram in the anterior posterior position and usually in both the left and right anterior-oblique positions (see Figure 11–14 and Chapter XII)

Enlargement of the ascending arch of the aorta in an adult usually causes a conspicuous shadow to the right of the sternum this shadow can usually be traced behind the sternum to the aortic knob It is, however noteworthy that marked dilatation of the ascending aorta may even in adults, be entirely concealed behind the sternum, as in the cases reported by Baer, Taussig and Oppenheimer [1]

Marked hypoplasia of the ascending aorta occurs in combination with atresia of the aortic orifice or with defective development of the left ventricle

Aortic atresia is rare but may occur in combination with defective development of the left ventricle Under such circumstances there is always great hypertrophy of the right side of the heart and of the pulmonary artery Consequently, the diminutive size of the ascending aorta may be difficult to demonstrate Furthermore, the infant is often so critically ill and the duration of life so short that only the briefest examination is possible The existence of marked hypoplasia of the ascending aorta is not directly observed by fluoroscopy The diagnosis is deduced from a combination of the physical findings and the fluoroscopic examination (see Chapter XIII)

A right aortic arch means that the aorta arches to the right instead of to the left The position of the aorta can be determined by x ray examination When

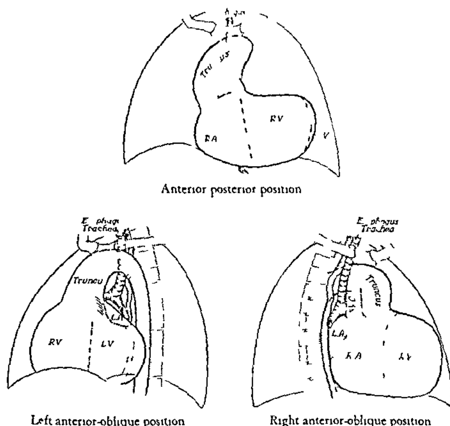
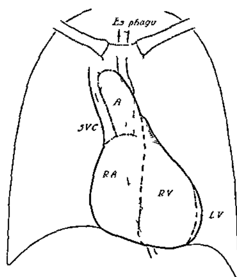
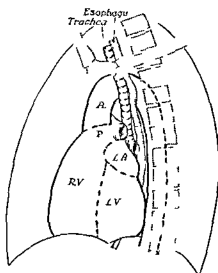


FIGURE 11-14 Truncus arteriosus Infant

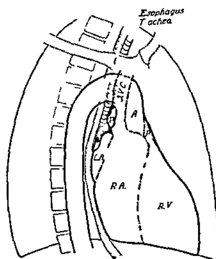
the aorta arches to the right it descends close to the spinal column and displaces the superior vena cava to the right Consequently, the aortic knob is frequently concealed within the broad ribbon like shadow of the superior vena cava [3] Nevertheless, careful examination usually reveals the shadow of the aortic knob within the shadow of the superior vena cava Visualization of the esophagus aids in the diagnosis because the aorta displaces the esophagus to the left and indents its right margin (see Figure 11-15 and Chapter xxvi) Furthermore the aorta no longer impinges upon the esophagus in the right anterior-oblique position The impingement may be seen in the left anterior-oblique position but this does not always occur because although the aorta descends upon the right the heart still occupies its normal position Although the anomaly is comparatively rare in malformations in which there is no cyanosis, it occurs in approximately 20 per cent of all malformations in which cyanosis is due to some abnormality of



Anterior posterior position



Left anterior oblique position



Right anterior oblique position

FIGURE II–15 Tetralogy of Fallot with a right aortic arch Adult

Note the course of the esophagus

the great vessels Therefore, the possibility should always be borne in mind and the determination of the course of the aorta should be a routine procedure

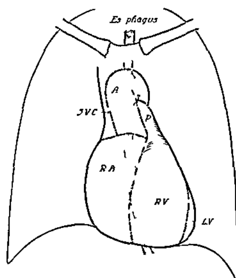
A right aortic arch combined with a left descending aorta causes a conspicuous change in the course of the esophagus When the aorta arches to the right and then descends upon the left, it crosses behind the esophagus and displaces it anteriorly Consequently, in the oblique positions the esophagus appears to lie in front of the shadow cast by the great vessels The abrupt deviation of the esophagus toward the anterior chest wall if sought for, is always readily visible (see Figure 11–16 and Chapter XXVI)

A retro-esophageal aorta may also occur when *a right descending aorta persists in combination with a normal left aortic arch* Under such circumstances the aorta arches to the left in the normal manner and then passes behind the trachea and esophagus to descend on the right This anomaly was first described by Paul[13] In the oblique views this condition causes an anterior displacement of the esophagus which is closely similar to that which occurs in a right aortic arch with a left descending aorta The two conditions however can be differentuated in the anterior posterior view When the aorta arches to the left, the aortic knob occupies its normal position on the left then the aorta passes abruptly to the right, posterior to the trachea and esophagus and consequently the esophagus courses downward along the left border of the sternum Upon delineation of the esophagus with a radio-opaque material, the esophagus can readily be seen to the left of the sternum, where it lies between the aortic knob and the upper border of the cardiac shadow, as shown in Figure 11–17

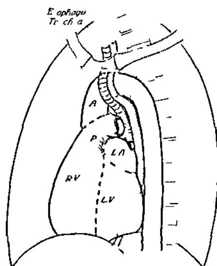
The innominate artery may occasionally pass behind the esophagus and cause a similar but less conspicuous distortion of the esophagus Moreover, since the innominate artery arises from the upper margin of the aorta anterior displacement occurs at a slightly higher level than that produced by the aorta

The right subclavian artery occasionally arises from the arch of the aorta and not from the innominate artery Under such circumstances it generally arises from the left side of the aortic arch and passes behind the esophagus and then along the right clavicle to the right arm Such an anomaly causes anterior displacement of the esophagus at or immediately above the arch of the aorta The indentation is however considerably smaller than that caused by a retro-esophageal aorta or even by the innominate artery It is the location and also the size of the indentation or the extent of displacement of the esophagus which give the clue to the diagnosis

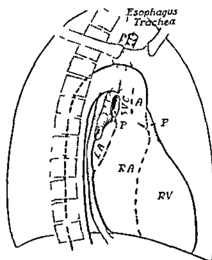
Retro esophageal vessels which course from the descending aorta to the lungs,



Anterior posterior position



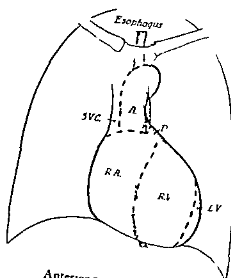
Left anterior-oblique position



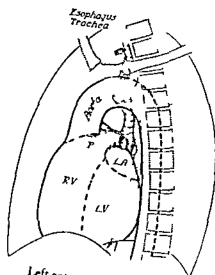
Right anterior-oblique position

FIGURE 11–16 Tetralogy of Fallot with a right aortic arch and a left descending aorta Adult

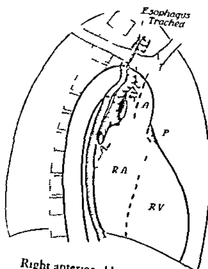
Note the course of the esophagus



Anterior posterior position



Left anterior-oblique position



Right anterior-oblique position

FIGURE II-17 Tetralogy of Fallot with a left aortic arch and a right descending aorta Adult

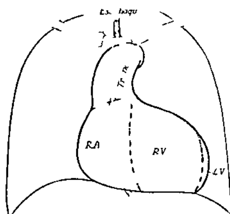
Note the course of the esophagus



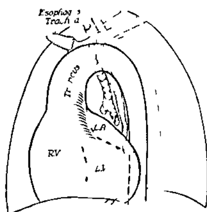
FIGURE II–18 Truncus arteriosus Child

Note displacement of the esophagus by a retro-esophageal vessel

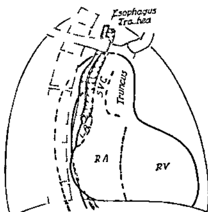
when sufficiently large, cause anterior displacement of the esophagus Because of the small size of these vessels and the angle at which they press upon the esophagus the displacement is frequently detected only in one oblique position Therefore, it must be carefully sought for in the right and in the left anterior oblique positions These vessels may be located at any level Such vessels may cause slight distortion of the esophagus as they press against it (see Figures II–14 and II–19), or the esophagus may be caught between two or more of the vessels and displaced in a bizarre manner (as shown in Figure II–18) When there is slight anterior displacement of the esophagus high up, such shadows may require differentiation from a retro-esophageal subclavian artery or from the innominate artery Localized anterior displacement of the esophagus in the lower thoracic region is usually indicative of an abnormally large bronchial artery which passes to the lungs behind the esophagus (see Figures II–14 and II–19 left anterior-oblique views) The demonstration of such vessels in combination with an abnormally prominent aortic knob is almost diagnostic of a truncus arteriosus (see Chapter XIV)



Anterior posterior position



Left anterior oblique position



Right anterior-oblique position

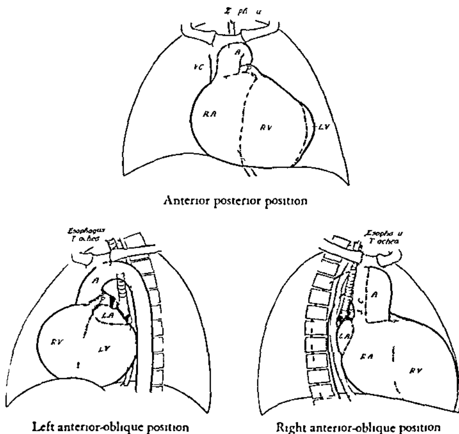
FIGURE II–19 Truncus arteriosus Child

Note the anterior displacement of the esophagus by a retro esophageal vessel in left anterior oblique position

ABNORMALITIES OF THE PULMONARY ARTERY

Pulmonary atresia causes an absence of the fullness of the pulmonary conus and a narrow aortic shadow Inasmuch as there is but one great vessel, the shadow cast by the single vessel is narrow both in the anterior posterior and in the left anterior oblique positions In the latter position, the absence of the pulmonary artery renders the pulmonary window abnormally clear (see Figures 11-6 and 11-20) The lack of the shadow normally cast by the pulmonary conus and the pulmonary artery causes a sharp angulation to the upper border of the cardiac silhouette in the right anterior-oblique position (Figure 11-20)

An abnormally small pulmonary artery causes a similar change in the contour of the heart In a tetralogy of Fallot the pulmonary stenosis is usually combined with an abnormally small pulmonary artery and a reduction in the size of



Anterior posterior position

Left anterior-oblique position

Right anterior-oblique position

FIGURE 11-20 Tetralogy of Fallot with severe pulmonary stenosis or pulmonary atresia Infant

the outflow tract of the right ventricle Consequently there is a concave curve at the base of the heart to the left of the sternum and a clear pulmonary window (see Chapter VI)

When the pulmonary artery is misplaced as it is in a *complete transposition of the great vessels* changes in the shadow cast by the great vessels are distinctive In this anomaly there is a rotation of the great vessels in a counterclockwise direction so that the aorta arises from the right ventricle and the pulmonary artery from the left ventricle The result is that the pulmonary artery comes to lie behind the aorta

In infancy, when the diaphragm lies at a high level the abnormal position of the pulmonary artery causes the shadow cast by the great vessels to appear abnormally narrow in the anterior posterior view In addition there is an absence of the fullness of the pulmonary conus This is due to the fact that the aorta seldom lies as far to the right as does the normal pulmonary artery Therefore the

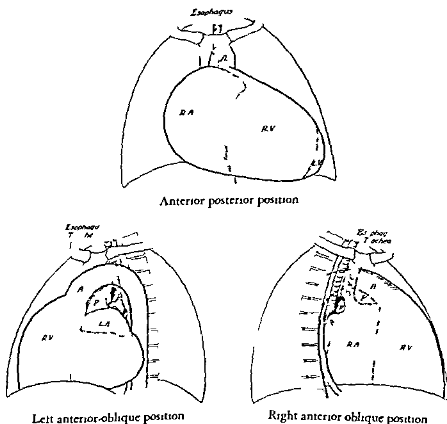
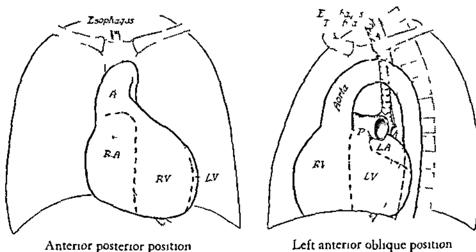


FIGURE II-21 Complete transposition of the great vessels Infant



Anterior posterior position Left anterior oblique position

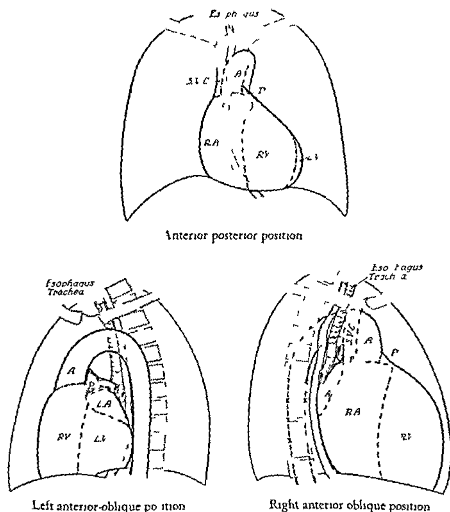
FIGURE 11–22 Complete transposition of the great vessels Child

shadow at the base of the heart to the left of the sternum is concave The contour of the heart in a case of complete transposition of the great vessels is shown in Figure 11–21

Upon rotation into the left anterior oblique position the two vessels come to be parallel to one another Consequently, the shadow cast by these vessels markedly increases in width By placing one finger behind the other and rotating the hand 45 , the cause of the increase in width of the great vessels becomes readily apparent (see Chapter x)

In children as the diaphragm descends the contour of the heart and great vessels changes These changes are due in part to the elongation of the great vessels and in part to the fact that only if the heart ceases to enlarge is the condition compatible with life for a number of years Therefore the heart, although slightly enlarged, is not huge Owing to the absence of the fullness of the pulmonary conus in the anterior posterior view its contour closely resembles that of a tetralogy of Fallot (compare Figures 11–22 and 11–23) Moreover, when the great vessels are transposed, the pulmonary artery instead of arching over the aorta as it normally does, passes directly posteriorly to the lungs The result is that as the heart comes to occupy a more vertical position, the pulmonary artery lies at an abnormally low level, consequently, in the left anterior oblique position there is no increase in the width of the shadow cast by the great vessels Thus, in contrast to the findings in infancy the aortic shadow remains narrow and the pulmonary window large and clear (see Figure 11–22 and Chapter x)

Partial transposition of the great vessels is more difficult to determine It is



Anterior posterior position

Left anterior-oblique position

Right anterior oblique position

FIGURE II-23 Tetralogy of Fallot Child

however usually associated with stenosis of the pulmonary artery and with obstruction in the outflow tract of the right ventricle, as in the tetralogy of Fallot Under such circumstances, in the anterior posterior position there is an absence of fullness of the pulmonary conus In the left anterior-oblique position the diminutive size of the pulmonary artery renders the pulmonary window abnormally clear In the right anterior oblique position the diminutive size of both the pulmonary artery and the outflow tract of the right ventricle produce a sharp concave angulation at the upper margin of the cardiac silhouette (see Figures II-20 and II-23 and also Chapter VI)

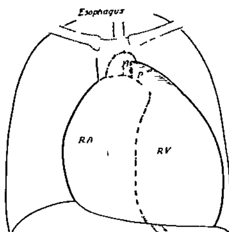
In brief, a concave curve at the base of the heart to the left of the sternum means that the pulmonary artery is absent, diminutive, or misplaced

The size of the pulmonary artery varies with the volume of the pulmonary blood flow and hence with the vascularity of the lung fields When the pulmonary blood flow is increased, the lungs appear excessively vascular, whereas when there is severe pulmonary stenosis and minimal circulation to the lungs, the lung fields are excessively clear

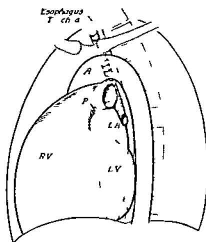
The vascularity of the lungs is therefore, extremely important By the examination of the lung fields and the hilar shadows it is possible to determine whether the pulmonary blood flow is approximately normal, markedly reduced, or greatly increased The pulmonary vessels, of course, increase in size with the growth of the individual so that the vascular markings must be judged relative to the age and the size of the patient The vascular markings are exaggerated when the pulmonary blood flow is increased and they are minimal when the pulmonary blood flow is markedly reduced Furthermore when the circulation to the lungs is excessive and the pulmonary resistance is low, the vascular markings extend far out into the lung fields, whereas when the pulmonary blood flow is approximately normal or but slightly increased and the resistance in the lungs is increased the pulmonary vessels rapidly decrease in size and the periphery of the lungs remains clear

Thus careful study of the pulmonary vascular markings gives valuable information concerning the volume of pulmonary blood flow This is true regardless of the position of the pulmonary artery and hence regardless of whether or not the patient is cyanotic

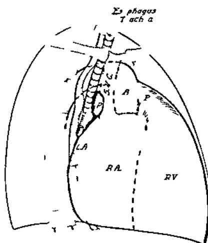
Dilatation of the pulmonary artery combined with prominence of the pulmonary conus means that the pulmonary artery is enlarged and is normally placed This may occur as an isolated anomaly Usually however dilatation of the pulmonary artery is associated with increased pulmonary blood flow and enlargement of the right ventricle (see Figure 11–24) The main pulmonary artery is also dilated when there is stenosis of the pulmonary valve and poststenotic dilatation of the pulmonary artery (see Figure 11–5) When there is enormous dilatation of the pulmonary artery both the left and the right branches of the pulmonary artery are greatly dilated, the vascular markings extend well out into the lung fields (see Figure 11–25) and there is usually a conspicuous hilar dance When there is pulmonary stenosis or pulmonary hypertension, although the pulmonary artery and its main branches may be greatly dilated and may even show definite pulsations, the periphery of the lungs remains clear



Anterior posterior position



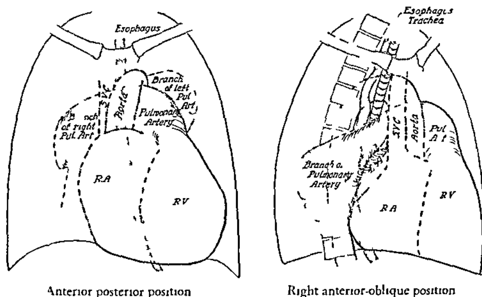
Left anterior-oblique position



Right anterior oblique position

FIGURE II–24 Large right ventricle (dilatation and hypertrophy) and dilated pulmonary artery Child

Prominence of the pulmonary conus also occurs when the aorta is trans posed far to the left and occupies the position of the normal pulmonary artery This may occur when there is a so-called corrected transposition that is a transposition of the ventricles with a rotation of the great vessels as shown in Figure II–26 (see also Chapter XXXI) and also occasionally when there is a com plete transposition of the great vessels with the aorta transposed far to the left and pulmonary stenosis as shown in Figure II–27 In the former instance the



Anterior posterior position Right anterior-oblique position

Figure 11–25 Enormous dilatation of the pulmonary artery Adult

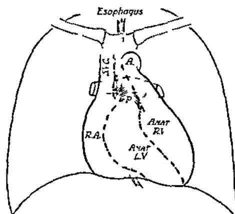


Figure 11–26 Corrected transposition of the great vessels Child

vascularity of the lungs is normal, and in the latter the lungs are excessively clear

Absence of the fullness of the pulmonary conus combined with excessive vascularity of the lungs and dense hilar shadows shows that although the pulmonary blood flow is increased, the pulmonary artery is misplaced Hence, it means that there is a complete transposition of the great vessels and a large posteriorly placed pulmonary artery

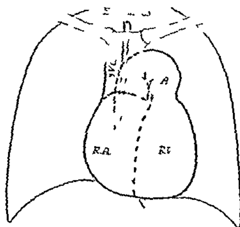


FIGURE II-27 Complete transposition of the great vessels with pulmonary stenosis and the aorta far to the left Child

The density of the hilar shadows varies with the position of the pulmonary artery with the volume of the pulmonary blood flow and with the extent of the collateral circulation When the pulmonary artery is normally placed and the pulmonary blood flow is increased the hilar shadows are conspicuous, and hilar pulsations when present are readily visible When the pulmonary artery is posteriorly placed, not only is there absence of the fullness of the pulmonary conus, but there is also a mass of lung tissue which lies anterior to the pulmonary artery and obscures these vessels

The extent to which the lung tissue may obscure the vascular structures is shown in Figure II-28 In this instance there was a congenital absence of the right lung and the overexpansion of the left lung completely obliterated the cardiac shadow , nevertheless the cardiac impulse was readily felt to the right of the sternum Under normal circumstances the lung tissue does not obliterate the pulmonary vessels but it does render their outlines less distinct Often the vascular markings appear as great blotchy hilar shadows

When the pulmonary artery lies deep within the chest many blood vessels are viewed on end as they course to the anterior portion of the lungs These vessels appear as a number of discrete circular shadows Such findings are characteristic of a complete transposition of the great vessels when both great vessels are of normal size The same findings also occur when a complete transposition of the great vessels is combined with a valvular pulmonary stenosis as under such circumstances the pulmonary arteries themselves are usually of normal size Such



Anterior posterior position



Right lateral position

FIGURE 11-28 Congenital absence of the right lung and over expansion of the left lung Infant

Note the absence of the cardiac shadow

vessels cause increased vascular markings which upon fluoroscopy may appear extremely dense in the hilar regions, in the x ray films the vascular markings will be seen to extend to the periphery of the lungs This finding clearly differentiates these shadows from those of collateral circulation

The development of collateral circulation especially when it occurs by way of the posterior mediastinal vessels also increases the density of the hilar shadows The development of collateral circulation goes hand in hand with the development of polycythemia Hence increased hilar shadows should never be attributed to collateral circulation in a patient with a normal red blood cell count In the absence of polycythemia an increase in the vascular markings is almost invariably due to an increase in the volume of blood in the pulmonary arteries and not to collateral circulation Pulsations in these vessels however may not be visible because of the abnormal position of the pulmonary artery

Hilar pulsations should always be sought for after the observer s eyes are well accommodated Therefore on routine fluoroscopy this is the last point in the examination Slight hilar pulsations are normally visible in older children and adults For this reason the extent of the hilar pulsations should be evaluated in relation to the age of the child and the size of the vessels Slight movement in these vessels is not to be confused with the expansile pulsations which occur in large pulmonary arteries associated with excessive circulation to the lungs

Hilar pulsations or the *so-called dancing hilus* occur when there is marked dilatation of the pulmonary artery and increased pulmonary blood flow The strength of the pulsations varies not only with the volume of the pulmonary blood flow but with the pulse pressure in the pulmonary artery that is with the magnitude of the difference between the systolic and the diastolic pressures in the pulmonary artery A conspicuous hilar dance is usually present when increased pulmonary blood flow is combined with a normally placed pulmonary artery in which the pressure is normal or slightly increased, as for example, in the Lutembacher syndrome or in anomalies of the venous return In a complete transposition of the great vessels not only is the main pulmonary artery deep within the chest and the main branches hidden behind the lung tissue but the diastolic as well as the systolic pressure in the pulmonary artery is elevated therefore, unless the pulmonary artery is tremendously enlarged pulsations in these vessels are seldom visible

In brief the study of the size and shape of the great vessels and of the vascular shadows gives valuable information concerning the structure of the heart and the volume of the pulmonary blood flow it also gives some indication of the resistance encountered in the lungs

Electrocardiography

The electrocardiogram is of great value in the analysis of malformations of the heart, it gives basic information which cannot be derived from x ray or *fluoroscopy The latter reveals the size and shape of the various chambers of the* heart and gives an indication of the volume of the pulmonary blood flow, but it does not help to differentiate cardiac dilatation from hypertrophy The electrocardiogram gives information concerning the relative thickness of the two ventricles and hence of the relative amount of work required of each This information is basic to the analysis of malformations of the heart, it is best obtained from the unipolar precordial leads The development of these leads by W H Craib of South Africa[14] and F N Wilson[15 17] has tremendously enhanced the information derived from the electrocardiogram For a detailed discussion of electrocardiography the reader is referred to the various authorities of the subject [18 3] The following discussion is concerned only with the basic electrocardiographic findings which are of aid in the analysis of malformations of the heart

The P waves give information concerning the auricles *High peaked P waves* of normal duration in congenital malformations of the heart are, in the author s experience, usually indicative of difficulty in the expulsion of blood from the right auricle High peaked *Himalayan* P waves (5 to 10 mm in height) are frequently seen in tricuspid atresia when there is only a small defect in the auricular septum *Broad high P waves* occur in cardiac malformations in which there is both an increase in the duration of the auricular contraction and an increase in the force of contraction Such P waves commonly occur when the right auricle pumps the blood into the right ventricle against increased pressure, as for example, when there is pulmonary stenosis or pulmonary hypertension We have called such waves *pyramidal* P waves as they resemble the pyramids

Notching and prolongation of P waves of normal amplitude frequently occur with hypertrophy of the left auricle, as is common in mitral stenosis

Inversion of the P waves in the standard leads indicates an abnormal origin of the auricular contraction[4] or a grossly abnormal position of the right auricle

The atrioventricular conduction time (the P R interval) is usually normal in patients with congenital malformations of the heart Nevertheless prolongation of the conduction time may occur in patency of the ductus arteriosus and in Ebstein s anomaly of the tricuspid valve it is also common in association with gross defects in the auricular septum In the last mentioned condition, however, if the conduction time is prolonged the possibility of a superimposed rheumatic infection should be considered

A right axis deviation is physiological in infancy and childhood Hence, unless accompanied by evidence of right ventricular hypertrophy in the unipolar precordial leads it should not be considered abnormal

A left axis deviation in a patient with persistent cyanosis is always suggestive of tricuspid atresia or gross underdevelopment of the right ventricle Indeed a left axis deviation is so rare in early childhood that its occurrence even in the absence of cyanosis is usually an indication for further studies [5, 6] However it is important to remember that the thickness of the left ventricle relative to that of the right normally increases with age, and consequently a left axis deviation occurs with increasing frequency in older individuals

Right ventricular hypertrophy is best determined in the precordial leads V_1 and V_{3R} The presence of a tall R wave in these leads is indicative of hypertrophy of the right ventricle The finding of an R–S ratio greater than 1 and a total duration of the QRS complex of less than 0 12 second is generally indicative of right ventricular hypertrophy A tall R wave in V_1 is usually accompanied by a deep S wave in V_5 and V_6 this finding is indicative of right ventricular dominance The finding in V_1 of a high R wave accompanied by a delay in the onset of the intrinsicoid deflection of more than 0 04 second combined with a slightly increased total duration of the QRS complex, and an inversion of the T wave, is indicative of extreme right ventricular hypertrophy It occurs frequently when the right ventricle pumps against an increased resistance This finding which was described by Cabrera and Monroy [7] as systolic over load ' of the right ventricle, is common in severe pure pulmonary stenosis and in pulmonary hypertension

Widening of the QRS complex in V_1 with an RsR^1 configuration and a duration up to 0 08 second may occur in normal infants and in young children Further notching or prolongation of the QRS complex is usually pathological Such polyphasic deflections are frequently seen when the right ventricle is required to pump an excessively large volume of blood as in an auricular septal defect or an anomaly of the venous return Under such circumstances there is dilatation as well as hypertrophy Complexes of this type are considered by Cabrera and Monroy[7] to be indicative of diastolic over load "

Left ventricular hypertrophy is best determined in the precordial leads over the left ventricle that is in V_5 and V_6 When there is left ventricular preponderance V and V_6 show a tall R wave which is usually preceded by a small Q wave and V_1 generally shows an increase in the depth of the S wave The latter, when present is confirmatory evidence of left ventricular dominance, but it is a less

constant finding With excessive left ventricular hypertrophy there is a delay in the onset of the intrinsicoid deflection of more than 0 04 of a second in V_5 and V_6, but the total QRS complex is not usually increased, the R wave progressively increases in height, and, in addition, there may be an inversion of the T wave combined with depression of the ST segment

Combined ventricular hypertrophy is indicated by the combination of tall R and deep S waves in V and V_6 Not infrequently there is a similar pattern of tall R and deep S waves in V_1 At times evidence of right ventricular hypertrophy is seen in V_1, and left ventricular hypertrophy in V_5 and V_6, this finding, too is usually indicative of hypertrophy of both ventricles Thus, the pattern of com bined hypertrophy is extremely variable Broadly speaking tall deflections in the precordial leads are usually indicative of increased thickness of the ventricular myocardium

Electrocardiography is also of prime importance in the diagnosis of a few specific conditions It offers proof of a complete heart block and of a true dextrocardia such as occurs with a situs inversus

Electrocardiographic signs of acute anterior myocardial infarction are found when the left descending coronary artery arises from the pulmonary artery [8] Therefore when such a pattern is seen in early infancy it is always strongly suggestive of this anomaly (see Chapter xxix)

Abnormally small deflections of relatively long duration in V_1 and V_3 combined with deflections of normal amplitude in V_5 and V_6, are characteristic of Ebstein s anomaly of the tricuspid valve [9] (see Chapter xix)

Evaluation of the Physical Examination Fluoroscopy and Electrocardiography

The final diagnosis of the nature of a cardiac malformation in an infant is made on a broad functional basis All the possible facts are collected The size and the shape of the heart are studied to determine the presence or absence of the various chambers and the degree of enlargement The size and position of the great vessels are studied in a similar manner Over a period of time, changes in the size of the heart relative to the growth of the infant are carefully evaluated The vascularity of the lung fields is carefully studied and all possible information is collected concerning the dynamics of the circulation The nature of the malformation is figured out by a process of stern logic The laws of physics and physiology are not to be violated For example, if the aorta or the pulmonary artery is to function it cannot arise from a chamber which does not function

Furthermore, life demands that the blood be pumped through both the systemic and the pulmonary circulations by means of the existing chambers of the heart and the arterial pathways It cannot be trapped in any chamber If there is pulmonary atresia, there must be some other way by which the blood can reach the lungs If there is tricuspid or mitral atresia there must be a defect in the auricular septum in order that the blood can escape from the auricle which lacks its normal outlet

If all factors are given due consideration a large number of severe malformations of the heart can be diagnosed on a broad functional basis In some malformations special tests such as cardiac catheterization and/or angiocardiography may be necessary for accurate diagnosis (see Chapter III) If however, the infant is doing well and growth and development are normal and the heart remains normal in size, early diagnosis of the nature of the malformation is not important In such instances it is advisable to keep the child under observation Frequently as the child grows signs and symptoms will develop which will permit the diagnosis to be established with certainty without resorting to further diagnostic procedures

The constant aim of medicine should be the simplest method of diagnosis which will give a high degree of accuracy

Summary

The existence of a congenital malformation of the heart is suggested by the detection of unusual murmurs and thrills by the presence of cyanosis and clubbing, or by alteration in the size shape, or position of the heart Accurate diagnosis of the nature of the malformation is frequently possible on the basis of the information derived from physical examination x ray fluoroscopy and electrocardiography

Physical examination gives an indication of the size of the heart and of its functional capacity In infants the heart is larger in proportion to the chest than it is in adults and murmurs are more widely transmitted Murmurs vary with the relative pressure in the systemic and pulmonary circulations Therefore although murmurs and thrills are often of diagnostic aid in adults in infants these findings serve only to direct attention to the heart They are seldom of value in the analysis of the nature of the malformation A loud, clear second sound at the base of the heart is suggestive of the existence of one great vessel Reduplication of the second sound is positive proof of the existence of both great vessels

Cyanosis and clubbing indicate that there is difficulty in the direction of an

adequate supply of oxygenated blood to the systemic circulation Cyanosis is usually indicative of a venous arterial shunt The distribution of the cyanosis may offer a clue to the course of the circulation

The presence of a strong femoral pulse excludes the existence of a coarctation of the aorta

The respiratory rate in infancy is a sensitive index to the state of compensa tion Rales in the lungs in cyanotic infants are always suggestive of adequate pul monary blood flow

Engorgement of the liver is an early sign of cardiac failure in young patients

Pulsations at the margin of the liver occur in tricuspid insufficiency and also in tricuspid atresia and a well formed auricular septum with a small opening between the two auricles

Fluoroscopic examination reveals changes in the size and shape of the heart and the great vessels which are of prime importance in the diagnosis of congeni tal malformations It is essential to study the contour of the heart in the anterior posterior position and in both the left and the right anterior-oblique positions

In the anterior posterior position the combined size of the two ventricles, the presence or absence of the fullness of the pulmonary conus, and the size of the right auricle are readily seen The contour of the upper left margin of the cardiac shadow gives valuable information concerning the size of the pulmonary artery and of the outflow tract of the right ventricle Prominence of the pulmonary conus usually means that the pulmonary artery is normally located and carrying its full quota of blood A concave curve at the base of the heart to the left of the sternum indicates that the pulmonary artery is diminutive, absent, or misplaced

Examination in the left anterior-oblique position shows the relative size of the ventricles Enlargement of the right ventricle is indicated by the projection of the cardiac shadow toward the anterior chest wall The amount of rotation necessary for the left ventricle to clear the spinal column gives an indication of the size of the left ventricle This position is also best for visualization of the ascending aorta In cases of pulmonary atresia the aortic shadow is narrow and the pulmonary window is abnormally clear

Examination in the right anterior-oblique position offers evidence of the course of the aorta and the size of the left auricle To determine these it is essen tial to delineate the esophagus with a radio-opaque mixture Enlargement of the left auricle causes backward displacement of the esophagus which persists during deep inspiration Backward displacement of the esophagus is almost always ac companied by some lateral displacement

The occurrence of a simple right aortic arch the combination of either a right aortic arch and a left descending aorta or a normal left aortic arch and a right descending aorta are readily differentiated by an esophagram Small retro-esophageal vessels can also be detected by this procedure

The size of the pulmonary artery varies with the volume of the pulmonary blood flow and hence with the vascularity of the lung fields Greatly increased vascularity of the lungs is indicative of increased pulmonary blood flow, whereas excessively clear lungs indicate that the pulmonary blood flow is reduced This is true regardless of the position of the pulmonary artery

When the pulmonary artery is normally placed dilatation of the pulmonary conus and increased vascular markings indicate excessive pulmonary blood flow Dilatation of the pulmonary conus also occurs when the aorta is transposed far to the left Under such circumstances the pulmonary vascularity is usually normal or decreased

The density of the hilar shadows varies with the position of the pulmonary artery, the volume of pulmonary blood flow, and the extent of the collateral circulation through the posterior mediastinal vessels

The hilar pulsations vary with the position of the pulmonary artery the volume of pulmonary blood flow and the pulse pressure within the pulmonary artery Such pulsations should always be sought for Pulsations in the main pulmonary artery are seen when there is a large left to-right shunt and also occasionally when there is pulmonary stenosis and poststenotic dilatation Pulsations in the hila of the lungs may or may not be visible when a complete transposition of the great vessels occurs in combination with a greatly dilated pulmonary artery

Electrocardiography adds valuable information which cannot be obtained by x ray or fluoroscopy as the precordial leads indicate the relative thickness of the two ventricles and hence the relative amount of work required by each ventricle

The size and shape of the P waves indicate the amount of work required of the auricles Inversion of P waves in the standard leads indicates an abnormal origin of the auricular contractions

Variation in the A–V conduction time occurs in certain malformations

A right axis deviation is physiological in childhood A left axis deviation in infancy and early childhood is always abnormal

The unipolar precordial leads indicate the relative thickness of the two ventricles V_1 and V_{3R} give evidence of the amount of work required of the right ventricle and V_5 and V_6 give the same information for the left ventricle

In addition, the electrocardiogram offers proof of a complete heart block and of a dextrocardia The pattern of acute anterior myocardial infarction in infancy is characteristic of the origin of the left descending coronary artery from the pulmonary artery The electrocardiogram is also of great aid in the diagnosis of Ebstein s anomaly of the tricuspid valve

The final diagnosis of the fundamental abnormality in most of the severe malformations of the heart is based upon the proper evaluation of the information obtained from physical examination, x ray, fluoroscopy, and electrocardiography The structure of the heart must be such as to permit the continuous circulation of the blood under the altered conditions

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CHAPTER III

SPECIAL DIAGNOSTIC PROCEDURES

ANGIOCARDIOGRAPHY, AORTOGRAPHY, AND CARDIAC CATHETERIZATION

SPECIAL diagnostic tests are sometimes necessary to determine the nature of the malformation It is, however, a mistake to assume that angiocardiography or cardiac catheterization or even a combination of the two procedures gives the diagnosis Both are aids to diagnosis, but neither is a substitute for a careful evaluation of the physical findings Neither procedure should be undertaken *without a knowledge of the patient s condition and the diagnostic* problem involved Both are of greatest value when undertaken to clarify some specific point In a very real sense the more accurate the initial clinical diagnosis, the greater is the information obtained from these procedures The final analysis of the information derived from these tests should be evaluated in conjunction with the condition of the patient and the physical findings

Angiocardiography

Angiocardiography is the visualization of the heart and great vessels by the injection of radio opaque material This is usually performed by an injection into the venous circulation In order to demonstrate the various chambers of the heart a radio-opaque substance in high concentration must be injected so rapidly that virtually all the material passes through the various chambers of the heart as a conglomerate mass only slightly diluted by blood Under such circumstances if a series of x ray pictures is taken with sufficient rapidity, it is possible to visualize the sequential filling of the various chambers of the heart In the normal heart the right auricle is delineated first, then the right ventricle, and next the pulmonary artery The normal visualization of the right side of the heart in the anterior posterior and lateral positions is shown in Figure III–1 A few seconds later the substance is returned in high concentration to the left auricle, the left ventricle, and then to the aorta, as shown in Figure III–2

This technique was first developed by de los Reyes Castellanos, and Pereiras[1] in Cuba for the diagnosis of congenital malformations of the heart It was introduced into this country by Robb and Steinberg[2] in the study of cardiovascular disease in adults and has been extensively used and further perfected by Suss-

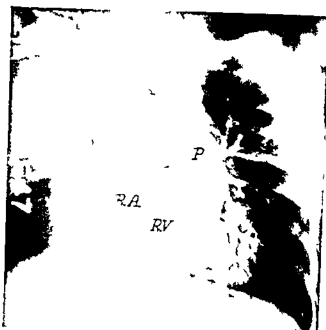




FIGURE III-1 Normal dextrogram Child



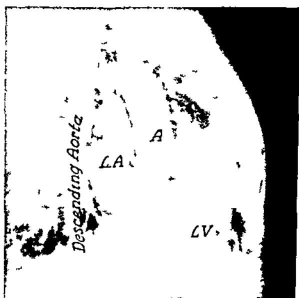


FIGURE III-2 Normal levogram Child

man Steinberg and Grishman[3] by Neuhauser and Jennings[4] by Dotter and Steinberg[5] and by others[6-10] When the accurate diagnosis of congenital malformations became of clinical importance, the technique was further perfected both here and abroad, especially in Sweden Many improvements have been made in the machine, the methods of changing cassettes, the speed at which the films can be taken, the method of injecting the radio-opaque material and the radio-opaque material itself Discussion of the technical problems is beyond the scope of this book For such information the reader is referred to the various authorities[11] This book is concerned with the clinical application of angiocardiography to the analysis of malformations of the heart and the great vessels

The delineation of the various chambers of the heart and the great vessels gives information concerning the size of the various chambers, the thickness of the walls the rate at which the dye circulates and the course which it follows It is above all the order in which the various chambers and the great vessels fill which aids in the diagnosis of congenital malformations of the heart

The rate at which the films are taken is extremely important In order to obtain any significant information it is essential to have the films taken at a rate of at least two per second and preferably three or four per second With some machines it is now possible to take eight, ten or even more frames per second When films are taken at a rate of three per second or faster, it is usually possible to differentiate between systole and diastole Obviously, for proper interpretation of any series of films it is essential to know both the order and the rate at which the films were taken

Broadly speaking when there is a shunt the more rapidly the films are taken and the longer the series the greater is the information obtained If, however, the circulation time is abnormally slow or if the visualization of the left side of the heart is desired it is equally desirable to be able to lengthen the time interval between exposures Therefore in order to take the films at the optimum time intervals it is essential to know the systemic circulation time and what specific abnormality is to be visualized

The pulmonary circulation time is usually so short, and our methods of measurement are so inaccurate that determination of the pulmonary circulation time is of little value The determination of the systemic circulation time is important in order to obtain optimum visualization of the aorta

Furthermore, it is usually desirable to obtain a series of films in both the anterior posterior and lateral positions This may mean that two series of films are necessary A machine has been perfected in Sweden which permits films to be

taken simultaneously in the anterior posterior and lateral positions, thereby eliminating the necessity of two injections

The radio opaque material used to delineate the course of the circulation is commonly spoken of as dye There are a number of such substances on the market, and new preparations are constantly being made in an effort to lessen the toxicity of the material and to improve the clarity of the pictures Neverthe less all such substances available up to 1960, when given in a sufficiently large amount and in sufficiently high concentration to delineate the chambers of the heart are toxic The dose varies with the preparation, it must always be regu lated according to the body weight of the patient and not according to the size of the heart

Difficulties arise when the heart is greatly enlarged Under such circum stances the dye is so greatly diluted by the increased volume of blood in the en larged chamber that it is difficult to visualize as it circulates through the heart Difficulties may also arise in the presence of a shunt, as the dye may be so rapidly dissipated to both the systemic and the pulmonary circulations that its subse quent course cannot be traced

The dangers in this technique are real and serious

Deaths have been reported in almost every clinic in which this technique has been extensively used The fatalities are remarkably few and notably less in non cyanotic than in cyanotic patients Nevertheless, there is always the possibility that the patient will develop ventricular fibrillation the instant the dye reaches the ventricle and therefore every angiocardiographic laboratory should be equipped with a defibrillator Most deaths, however, are due to hypersensitivity or to the toxicity of the drug

The possibility of hypersensitivity should never be forgotten Because of this danger it is a wise precaution to give the patient a small test dose prior to the first injection Furthermore the patient should be retested if there has been a lapse of weeks or even of several days between the successive angiocardiograms as sensitivity may have developed from the previous test Needless to say, a pa tient who has had a severe reaction to one injection should not receive another

It is extremely important to remember that adequate time must be allowed for the elimination of the dye between successive series of angiocardiograms With good kidney function it requires fully an hour to excrete all the dye there fore, this amount of time should always elapse between two injections Even though the material is rapidly excreted the effect of the dye appears to be cumu lative It has been the repeated experience almost everywhere that the risk of a

fatal reaction is increased by repeated injections For this reason more than two injections should never be given in one day This precaution is especially important to bear in mind in case of technical errors for example if the films jam or the patient moves Under such circumstances although there is a natural desire to repeat the procedure immediately in order to obtain a good picture, this should never be done when the difficulty occurs at the time of the second injection

The reactions are apparently of two types [1] an early immediate reaction and a late or delayed reaction The early reaction is in the nature of hypersensitivity or excessive toxicity If a large amount of dye passes directly up the carotid arteries to the brain it may cause convulsions, coma and death The delayed reactions are due to slow excretion of the dye Therefore, it is important to maintain fluid intake after the procedure If vomiting occurs intravenous fluids are indicated

The greatest danger of toxic reactions seems to occur in those malformations in which dye lingers for a long time in the right ventricle[13] and in those in which the circulation of the dye through the lungs cuts off the supply of oxygen to the individual Consequently, the procedure is especially dangerous in extreme pulmonary stenosis and in cor pulmonale It is also dangerous in any patient in whom the oxygen saturation of the arterial blood is extremely low Further, it is important to remember that a parent feels worse if a child dies in an effort to ascertain whether or not he can be helped than if he dies from an operation undertaken to save his life It is indeed tragic to lose the child and obtain a film which shows that an operation might have saved the child s life For these reasons angiocardiography is *contraindicated* in an extremely ill cyanotic child who suffers from a great reduction in the oxygen saturation of the arterial blood it is also contraindicated in severe cor pulmonale

The rapidity with which the dye is injected greatly affects the clarity of the pictures If the injection is made too slowly, the dye becomes so diluted with blood that tracing its circulation through the chambers of the heart may be impossible The apparatus for the rapid injection of dye developed by Keith and Munn[14] markedly lessens this difficulty

In adults it is highly desirable to take the films during deep inspiration, and obviously the patient must remain still throughout the procedure Since the dye causes flushing and a sensation of great heat the patient is likely to move as the dye reaches the systemic circulation Consequently his cooperation is a real asset In infants or young children, however the chest is so thin walled that the phase

of respiration is less important, and the circulation is so rapid that the coopera tion of the patient is not essential

The information derived from angiocardiography as previously stated per tains to the order of filling of the various chambers and the great vessels the length of time the dye lingers in any place, the size of the several chambers, and the thickness of their walls It is usually possible to visualize the sequential filling of the chambers of the heart up to the location of the first abnormality, be it a constriction or a shunt Thereafter, the lingering of the dye in one chamber or its dissipation in two or more directions frequently renders it difficult to trace the subsequent course of the dye

Anomalies of the superior vena cava are usually well demonstrated Inas much as a left superior vena cava is not rare in malformations which cause per sistent cyanosis, it is usually desirable to inject the dye into the left brachial vein or the left jugular vein Thereby, the left superior vena cava, when present, is readily delineated It may join the right superior vena cava or it may open di rectly into the coronary sinus (as shown in Figure III–3) or into the posterior wall of the right auricle Although the abnormal point of entrance of the supe rior vena cava into the right auricle does not alter the course of the circulation, knowledge of the existence of this abnormality is extremely important if open heart surgery is to be undertaken Occasionally, the two superior venae cavae open into different auricles the right superior vena cava opens into the right auricle in the normal manner (Figure III–1), and the left superior vena cava opens into the left auricle (as shown in Figure III–4)

Absence of the inferior vena cava is extremely rare when both the heart and the abdominal viscera occupy their normal positions Nevertheless, it does occur (see Chapter XXXII) The absence can be readily demonstrated by angiocardiog raphy or by cardiac catheterization if either of these tests is performed through the saphenous vein Under such circumstances the catheter follows an abnormal course (as shown in Figure III–5)

Anomalies of the right auricle are usually relatively easily demonstrated In the presence of a large auricular septal defect dye may pass into the left auricle which is opacified simultaneously with the right auricle (as shown in the upper plate of Figure III–6) this is commonly seen in tricuspid atresia Usually, how ever, the left auricle is not completely delineated but dye may be seen to pass from the right auricle through the defect into the left auricle (as shown in the lower plate of Figure III–6) In other instances the reverse may be true the shunt from left to right may be so large that there is an area in the right auricle oppo-

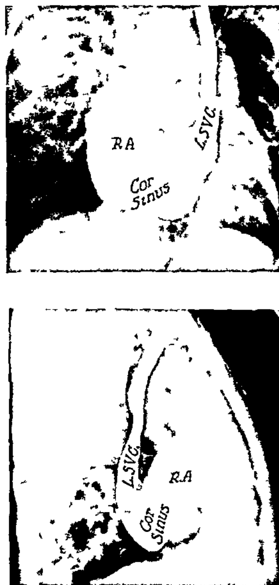


FIGURE III-3 Anomalous drainage of the left superior vena cava into the coronary sinus Child

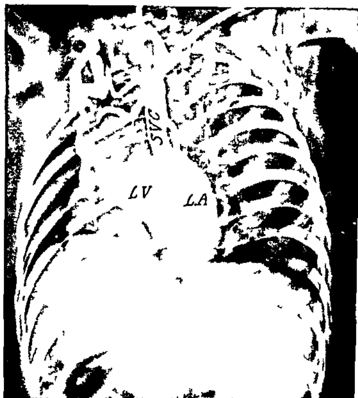
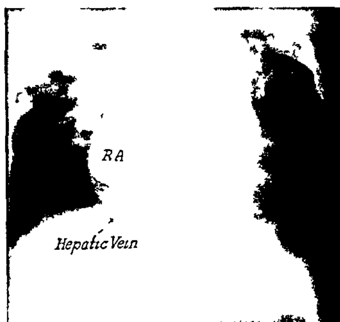


FIGURE III–4 Anomalous drainage of the left superior vena cava into the left auricle Child

site the defect in which the dye is displaced or diluted so as to cause a temporary filling defect This is usually best seen in the anterior posterior view (see Figure III–7) When the defect in the auricular septum lies high up in the septum close to the entrance of the superior vena cava, dye may pass from the superior vena cava into both auricles (as shown in Figure III–8) Such a high auricular defect is frequently associated with a partial anomaly of the venous return in which the upper right pulmonary veins drain into the right auricle at its junction with the superior vena cava In this type of *partial anomaly of the pulmonary venous return* angiocardiography frequently reveals an indentation at the margin of the right auricle due to the displacement of the dye by the entrance of blood into the right auricle from the pulmonary veins (as shown in the upper plate of Figure III–9) Occasionally if the pressure in the right auricle is unduly high dye may pass from the right auricle into the pulmonary vein (as shown in the lower plate of Figure III–9) In Ebstein s anomaly of the tricuspid valve dye may linger for a long time in the greatly enlarged right auricle Figure III–10



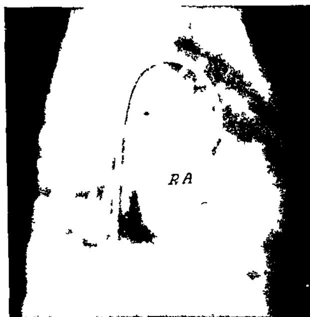
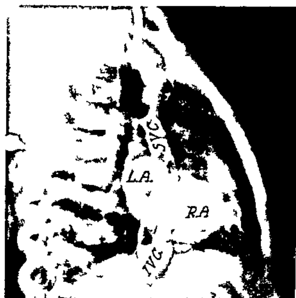


FIGURE III–5 Absence of inferior vena cava Child
Note the abnormal course taken by the catheter



Left auricle filled with dye Infant



Arrow points to dye passing to the left auricle Adult

FIGURE III–6 Auricular septal defect

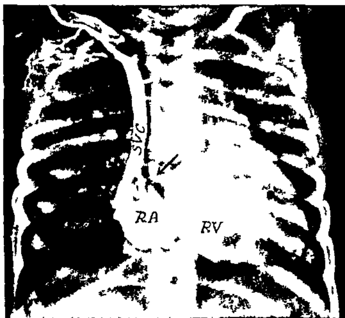


Figure III-7 Auricular septal defect Child
Arrow points to filling defect

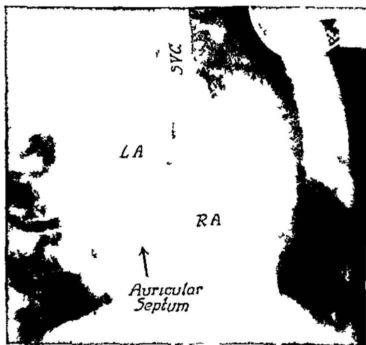
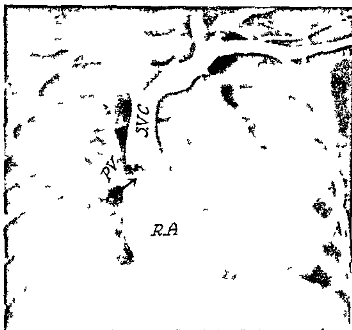


Figure III-8 High auricular septal defect Adult
Note dye passing from superior
vena cava into both auricles



Filling defect caused by blood entering the right auricle



Dye passing from the right auricle into the pulmonary vein

FIGURE III–9 Anomalous return of the right upper pulmonary vein to the right auricle Child

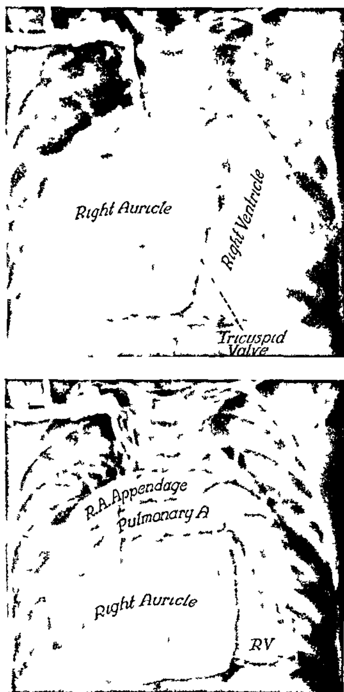


FIGURE III–10 Huge right auricle in a suspected Ebstein's anomaly of the tricuspid valve Child

illustrates enormous enlargement of the right auricle in a patient suspected of Ebstein's anomaly of the tricuspid valve In this instance the right auricle was so large that it was not entirely filled with dye, but the location of the tricuspid valve to the left of the mid sternal line is clearly visible

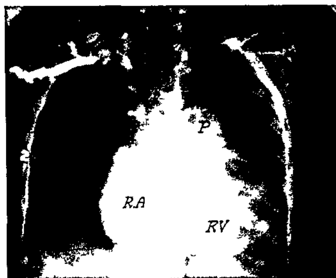
The right ventricle is usually well visualized (as in Figure III–1), and thereby information can be gained about its size, the thickness of the ventricular wall, whether there is difficulty in the expulsion of dye from the right ventricle, and whether there is early visualization of the aorta Failure to visualize the right ventricle is indicative of tricuspid atresia

The pulmonary artery normally arises from the right ventricle Under normal conditions the main left and right branches of the pulmonary artery fill promptly, and the dye passes rapidly to the lungs (as shown in Figure III–1) In valvular pulmonary stenosis with an intact ventricular septum, the pulmonary artery is promptly visualized, and thereafter the dye lingers for a long time in the main pulmonary artery and its branches (as shown in Figures III–11 and III–12, in which the dye is still visible in the pulmonary artery in the film taken seven seconds after the injection of the dye) Although such a finding is characteristic of pure pulmonary stenosis, the same finding occurs in cor pulmonale because the increased resistance in the periphery of the lungs greatly retards the flow of blood

Dextroposition of the aorta or transposition of the aorta can usually be well demonstrated because there is prompt visualization of the aorta simultaneously with or prior to visualization of the pulmonary artery (see Figures III–13, III–14 III–15) In the lateral view the aorta is seen to arise from the extreme anterior portion of the ventricle (see Figures III–14 and III–15) When the aorta arises in part or entirely from the right ventricle there is early dense visualization of the aorta followed by prompt emptying of the aorta In contrast to this when there is patency of the foramen ovale, as in pulmonary stenosis with an intact ventricular septum there may be faint prolonged visualization of the aorta, but dye never appears in great concentration in the aorta, whereas dye in high concentration lingers in the pulmonary artery for a long time Therefore angiocardiography may be of aid in the differentiation of a tetralogy of Fallot from pure pulmonary stenosis In a patient with a tetralogy of Fallot angiocardiography does not, however, give reliable information concerning the size of the pulmonary artery At times the pulmonary artery may appear relatively large and at operation be found to be extremely small The reverse may also occur the pulmonary artery may appear very small whereas in reality it is relatively large



At one second



At two seconds

FIGURE III–11 Pure pulmonary stenosis Child



At four seconds



At seven seconds

FIGURE III-12 *Pure pulmonary stenosis (series from Figure III-11 continued)*
Note dye still visible in the main pulmonary artery at seven seconds

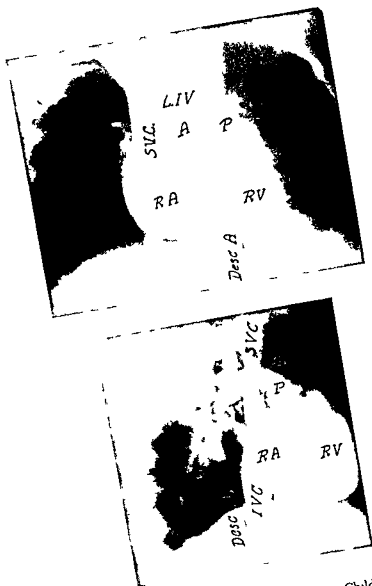


FIGURE III-13 Tetralogy of Fallot Child

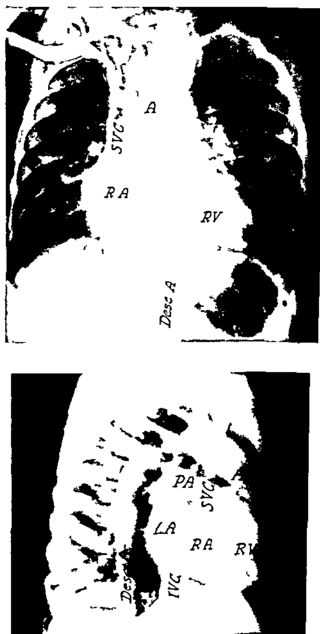
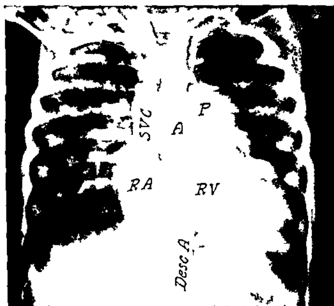


FIGURE III-14 Complete transposition of the great vessels Infant



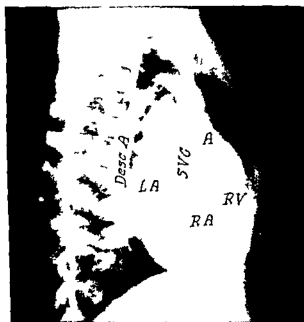


FIGURE III–15 Taussig Bing malformation Child

Note the pulmonary artery is concealed by the aorta in the lateral view

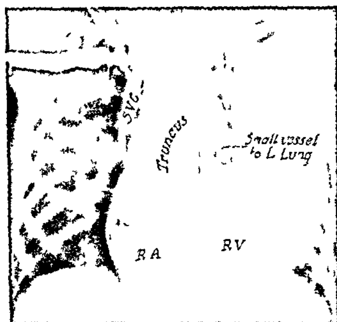
Furthermore when there is pulmonary atresia, dye obviously cannot pass from the right ventricle directly to the lungs Under such circumstances the amount of dye visualized in the lungs will depend upon the size and the location of the vessels of the collateral circulation

A truncus arteriosus with reduced pulmonary blood flow shows prompt opacification of the truncus immediately after the dye enters the right ventricle (see Figure III–16) Occasionally, the anomalous vessels of the collateral circulation may be demonstrated but generally this is not possible Consequently, it is frequently impossible to differentiate a truncus arteriosus with reduced pulmonary blood flow from a tetralogy of Fallot with pulmonary atresia

A truncus arteriosus in which the pulmonary arteries arise directly from the aorta is *extraordinarily difficult to demonstrate by angiocardiography* Although all the dye from the right side of the heart is pumped into the common trunk, it is immediately mixed with a large quantity of blood from the left side of the heart, and moreover the dye is rapidly dissipated to the lungs and to the body Consequently, it is frequently impossible to trace the dye beyond the right ventricle and yet it does not linger there

Malformations of the left side of the heart are usually well visualized only if there is no major abnormality on the right side of the heart In the presence of *extreme mitral stenosis* or *severe mitral insufficiency* (see Figure III–17) dye may linger for a long time in the left auricle The lower plate of Figure III–17 shows a large left auricle and a relatively thick walled left ventricle Sometimes in such extreme cases the left ventricle and the aorta are not visualized Opacification of the left ventricle gives information concerning the size of that ventricle and the thickness of its wall Moreover, if the films are taken sufficiently rapidly one can see the change in the size of the ventricle from systole to diastole For example, in a case of aortic stenosis with great hypertrophy of the wall of the left ventricle (see Figure III–18) a distinct change in the size of the ventricle between systole and diastole can be seen, in contrast to this, when the left descending coronary artery arises from the pulmonary artery, the left ventricle becomes enormously dilated the wall is extremely thin (see Figure III–19) and there is virtually no change in the size of the cavity in the various phases of the cardiac cycle

Coarctation of the aorta usually occurs as an isolated malformation Under such circumstances the course of the circulation is normal until it reaches the aorta *Therefore it is usually possible to demonstrate the location and the length*



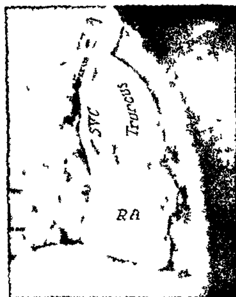
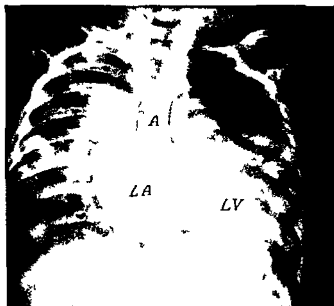
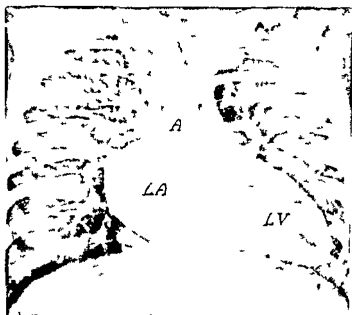


FIGURE III-16 Truncus arteriosus with reduced pulmonary blood flow Child

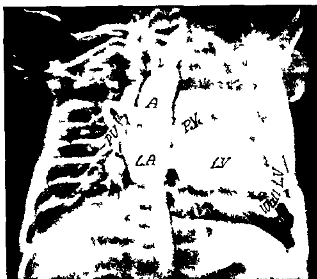


Congenital mitral stenosis Infant



Congenital mitral insufficiency Child

FIGURE III-17 Enlargement of the left auricle



In diastole



In systole

FIGURE III-15 Aortic stenosis with thick walled left ventricle Infant

Arrow points to the aortic stenosis



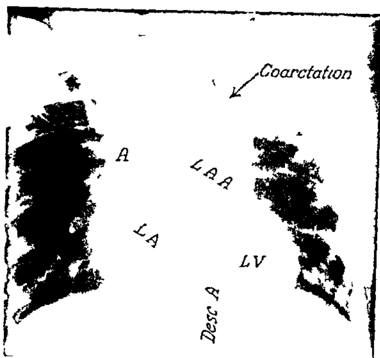
FIGURE III-19 Huge thin walled left ventricle due to an anomalous origin of the left coronary artery from the pulmonary artery Infant

of the constriction in the aorta Figure III-20 shows a coarctation of the aorta of the adult type and Figure III-21 one of the infantile type

Selective angiocardiography has been developed by Chavez et al [15] in order to trace the course of the circulation more accurately Selective angiocardiography means that the dye is injected through a catheter placed within the heart at the optimum point for the delineation of some specific feature

Although a smaller amount of test material is used when the dye is injected directly into the heart than when it is injected into a vein, the technique is not without danger as there is less dilution of the dye by the blood The greatest danger is that the catheter may pierce the endocardium, and the dye may be injected into the myocardium Although such accidents are remarkably well tolerated they are certainly to be deprecated No tests are devoid of risk In this instance the information gained is frequently well worth the risk involved

Dye may be placed in the right ventricle in order to determine whether or not the aorta arises from that chamber thereby the possibility of a shunt at the auricular level is eliminated Under such circumstances if the aorta is visualized from the right ventricle it is obvious that blood from the right ventricle can enter the aorta The injection of dye directly into the right ventricle also gives the best delineation of the outflow tract of the right ventricle and thus gives accurate



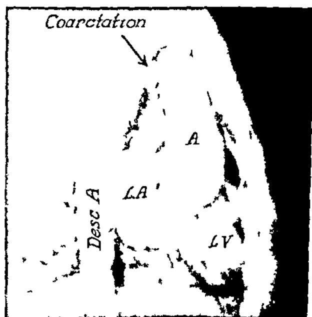


FIGURE III–20 Coarctation of the aorta of the adult type

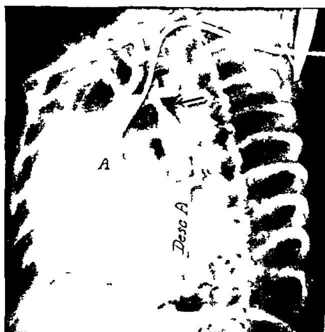


FIGURE III–21 Coarctation of the aorta of the infantile type

Arrow points to the coarctation

information concerning the presence and size of an infundibular chamber (see Chapter VI) Similarly *dye may be placed in one of the pulmonary arteries* in order to determine whether the pulmonary veins from that lung enter the right auricle or the left

The injection of dye into the left auricle may aid in the differentiation of an ostium secundum defect from an ostium primum defect because when the left auricle is completely filled the lower rim of the auricular septum if present, can usually be discerned (see Chapter XXIII, Section B)

It is sometimes possible *to pass the catheter from the left auricle to the left ventricle* and thereby obtain angiocardiograms of the left ventricle and the vessel or vessels which arise therefrom Angiocardiograms of the left side of the heart may also be obtained by the retrograde passage of a catheter from an artery back to the base of the aorta and through the aortic valve into the left ventricle The *injection of dye directly into the left ventricle* is the best technique for the visualization of ventricular defects in which the shunt is from left to right, furthermore such an angiocardiogram reveals whether the blood is shunted into the right ventricle or into the right auricle The injection of dye into the left

ventricle also clearly delineates the relation of the aorta to the left ventricle and shows abnormalities of the aortic orifice

Selective angiocardiography, however, gives limited information For example, angiocardiography will not reveal the presence of an auricular septal defect when the dye is injected into the right ventricle For such a technique to be helpful the clinical diagnosis must be relatively accurate For this reason, selective angiocardiography is of greatest value to confirm a diagnosis or to delineate a specific portion of the heart

Cineangiocardiography was first developed by Janker[16] in 1936 and has been perfected by Sones[17] especially for use in infants with malformations of the heart By this technique one can actually see the blood as it circulates through the heart, study the action of the heart and the valves, and visualize the direction of a shunt under specific controlled conditions The technique has the disadvantage that one cannot view several screens simultaneously and compare what is visible at one second with what occurs a fraction of a second earlier or later Furthermore, cineangiocardiograms do not give as much detail as do separate angiocardiographic films It is often only by careful study of an angiocardiogram that all the details in a single film are appreciated and the full value of the information revealed in the angiocardiogram obtained

The technique requires a special machine for viewing the cineangiocardiographic reel Consequently it is not as useful for teaching and study as a series of angiocardiograms which the student can study quietly by himself for as long as he desires and compare one picture with another

This specialized technique gives a beautiful demonstration of the blood as it circulates and opens up a new avenue for the study of the heart Nevertheless, great experience and keen observation are required to detect any new and unsuspected abnormality Therefore its greatest use lies in the confirmation of a diagnosis in the visualization of the action of the heart and in research studies

Aortography

Aortography is the visualization of the aorta by the injection of radio-opaque material directly into the systemic circulation

The test material must be injected under high pressure Since the dye must be forced into the aorta in the opposite direction of the flow of blood the force of the injection must be greater than the systolic pressure in the systemic circulation Keith et al[18,19] have devised an excellent apparatus with the necessary safety valves which permits the rapid injection of dye under high pressure This

technique is extremely satisfactory for aortography in infants, it removes the necessity of passing a catheter into the aorta and thereby lessens the inherent danger of the technique Needless to say if the visualization of the aortic arch and the ductus arteriosus is desired the films must be taken in rapid succession immediately upon the injection of the dye, as the blood which is ejected from the left ventricle flows through the arch of the aorta with great rapidity

The injection is always made on the left side, generally through the left carotid or the left brachial artery During the procedure the carotid arteries distal to the point of the injection should be momentarily occluded to prevent the passage of dye to the brain If the injection is made on the right side, in spite of this precaution all the dye may be carried up the carotid vessels to the brain Indeed the dye may pass so rapidly and so completely to the brain as to give the appearance of a complete interruption of the aorta when none exists

In order to obtain a satisfactory aortogram in children and adults it is usually necessary to pass a catheter through an artery, either the femoral or the radial artery, to the base of the aorta In this way the entire arch of the aorta can be visualized

The danger of injury to the brain from aortography is real Every preparation of radio-opaque material available in 1960 is toxic If a large amount of such a material reaches the brain, convulsions, coma, and death may result Therefore, precautions should always be taken to check the exact position of the catheter by fluoroscopy, furthermore during the injection the carotid arteries should be momentarily occluded Even with these precautions the danger of injury to the brain is so serious that an extremely high concentration of 70 per cent radio-opaque material should never be used Even if the patient has had an angiocardiogram with no untoward symptoms it does not mean that he can tolerate a similar dose injected directly into the cerebral vessels The procedure does not appear to be unduly dangerous if the concentration of the material is regulated according to that which has proved safe for cerebral angiocardiography Excellent visualization of the aorta in infants and young children can be obtained with such concentrations

Aortography properly performed, gives a beautiful visualization of the aorta and the vessels which arise from the aorta Therefore, this technique is of great value in the demonstration of the location and the length of the constriction in a coarctation of the aorta

Aortography is also of great help in the demonstration of a communication between the aorta and the pulmonary artery Under such circumstances dye in

jected into the aorta immediately passes through that opening into the lungs consequently the aorta and the pulmonary vessels are simultaneously visualized (as shown in Figure III–22) This test has proved extremely useful in the demonstration of patency of the ductus arteriosus especially in young infants who do not have a continuous murmur Simultaneous visualization of the aorta and pulmonary arteries also occurs if there is an aortic septal defect or a true truncus arteriosus Consequently, these three conditions may require differentiation from one another At times the aorta is so sharply delineated that the exact position of the communication can be seen If this is not possible, cardiac catheterization as well as aortography may be necessary to establish a diagnosis

Occasionally aortography may aid in the demonstration of the anatomical cause of a diastolic murmur If there is an aortic insufficiency the left ventricle will be promptly visualized, whereas if there has been a rupture of an aneurysm from the right sinus of Valsalva into the right auricle or the right ventricle that chamber will be visualized

Coronary arteriography has been perfected by Dotter and Frische [0] These investigators have devised a method by which the aorta is momentarily occluded at the time of the injection of the dye into the coronary arteries This technique gives beautiful visualization of the coronary vessels It is useful primarily in adults with disease of the coronary arteries It may well be the best means for exact diagnosis of coronary arteriovenous fistulae (see Chapter XXIX) Obviously the clinical diagnosis must be relatively accurate before this technique is employed

Further advances in the technique for the demonstration of various abnormalities will undoubtedly be developed The more specialized the technique the more accurate must be the clinical diagnosis before the special technique is utilized For this reason, such techniques may offer strong confirmatory evidence but will probably not be the methods of choice for the initial diagnosis

Cardiac Catheterization

Dr Werner Forssman, a German urologist was the first to pass a catheter into the heart *He had the courage to perform the experiment upon himself* He sat in front of a fluoroscope slipped a ureteral catheter into his brachial vein and watched it pass into his heart Moreover, he did it twice to prove to his colleagues that it was not a dangerous procedure That was in 1929

Andre Cournand [1] envisioned the tremendous possibilities for the advancement of physiological knowledge offered by this technique and he together

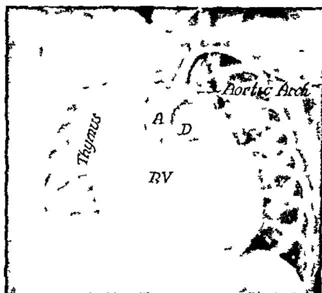




FIGURE III-22 Aortogram showing patency of the ductus arteriosus Infant Note dye passing from the aorta to the pulmonary artery

with Dickinson Richards, developed and perfected the technique of cardiac catheterization This method of investigation has contributed so greatly to our basic knowledge of cardiac physiology that these three doctors were awarded the Nobel prize for medicine and physiology in 1956

Although the initial delay between Forssman s experiment and Cournand s and Richards development of the technique of cardiac catheterization was long once the technique had been proved both safe and useful, it was rapidly adopted by others Indeed, it has become an accepted method of cardiac investigation Bing et al,[3] Dexter et al,[4] Wood et al, and others both in this country and abroad have added greatly to our knowledge of the physiology of congenital malformations of the heart

Cardiac catheterization involves passing a small catheter through one of the large veins usually the brachial vein, into the right side of the heart This procedure renders it possible to obtain samples of blood and pressure tracings from the various chambers into which the catheter passes For details of technique the reader is referred to the various authorities

It is important to appreciate that the exact position of the catheter, even with the aid of fluoroscopy, cannot always be determined with certainty Inasmuch as fluoroscopy gives a two dimensional image of a three dimensional object even in the normal heart there may be some question as to the exact position of the catheter Accurate determination of the position of the catheter is far more difficult in the malformed heart Moreover in the presence of a shunt it is impossible to determine whether the catheter lies directly in the center or at the periphery of the stream of blood entering the chamber X ray pictures taken to show the position of the catheter at the moment the determination is made increase the validity of the information obtained but such spot films should not be considered infallible

Cardiac catheterization should not be lightly undertaken although when properly done the risk is remarkably slight nevertheless the test is not without danger Deaths have been known to occur during and immediately after the procedure Strict asepsis must be observed It is always a wise precaution to give some antimicrobial agent in therapeutic doses for the ensuing twenty four hours Occasionally in cyanotic patients air emboli may be introduced and cause a hemiplegia Fortunately however even though the hemiplegia may be severe, the patient usually recovers without residual paralysis as the tissues are not deprived of oxygen by the embolus The manipulation of the catheter especially in the region of the tricuspid valve and in the right ventricle, may initiate an arrhyth

mia For this reason a continuous electrocardiographic recording should be made throughout the procedure Should any untoward reaction occur the procedure should immediately be terminated Inasmuch as patients occasionally develop ventricular fibrillation the instant the catheter touches the right ventricle, every catheterization laboratory should always have a defibrillator available for immediate use Fortunately such accidents are rare With reasonable precautions, the procedure is usually well tolerated, and much useful information can be obtained

In addition to arrhythmias in patients with severe pulmonary stenosis, the passage of the catheter through the pulmonary valve may occlude the pulmonary orifice and cut off the circulation to the lungs, thereby causing a severe drop in the oxygen saturation of the blood in the pulmonary artery

Finally, it should be remembered that when a large number of samples of blood are taken from a small infant the procedure may be the equivalent of a venesection Therefore a small infant should be given a transfusion during or immediately after the procedure This is especially important if prior to catheterization the infant had an anemia

Analysis of the oxygen content of the blood obtained from various places within the heart offers a clue to the structure of the heart The oxygen content of the blood in the inferior vena cava is generally higher than of that in the superior vena cava When the catheter is passed below the diaphragm as it approaches the renal veins, the oxygen content of the venous blood is increased, therefore, an effort should be made to obtain the sample at the level of or just above the diaphragm The sample should, however, be taken below the cardiac shadow, as the oxygen content of the blood returned to the coronary sinus is extremely low [8] Consequently, if the sample of right auricular blood is taken near the orifice of the coronary sinus, it too may be abnormally low Inasmuch as even in the normal individual, the oxygen content of the blood may vary in different parts of the same chamber, whenever it is possible it is desirable to take several samples of blood from each chamber In the absence of a shunt the average of the samples of blood taken from the two venae cavae and the right auricle gives the oxygen content of the so-called *mixed venous blood* In the normal heart the oxygen content of the blood is approximately the same throughout the right side of the heart When there is a normal hemoglobin (15 gm per 100 cc) the oxygen content of the blood is approximately 14 volumes per cent in the superior vena cava, in the right auricle, in the right ventricle, and in the pulmonary

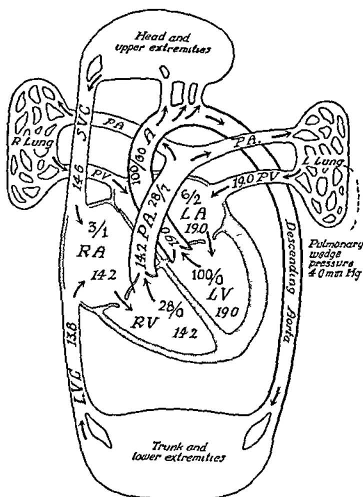
artery (see Figure III–23) If the hemoglobin is low, the oxygen capacity of the blood is reduced and the oxygen content of the blood is proportionately lower

Slight variations in the oxygen content of blood obtained from auricular samples should not be considered of great importance because of the normal variation in the oxygen content of the venous blood returned to the right auricle and also because of the possibility of laboratory errors In many laboratories variations in the oxygen content of the blood of less than 2 volumes per cent are not considered significant If, however, the oxygen content of the venous blood is abnormally high or that of the arterial blood abnormally low, the difference between the oxygen content of the arterial and venous blood may be only 3 volumes per cent Under such circumstances an increase of 2 volumes per cent represents a 66 per cent increase It is equally obvious that slight errors in technique may invalidate the values Therefore, the results of cardiac catheterization should be interpreted with care

In general, if the oxygen content of the sample of blood from the right auricle is more than 2 volumes per cent higher than that obtained from the superior vena cava, it is strong evidence either that there is an auricular septal defect or that some of the pulmonary veins enter directly into the right auricle Similarly, when the oxygen content of the blood in the right ventricle is significantly higher than of that in the right auricle, it is strong presumptive evidence of a ventricular septal defect

The oxygen content of the blood in the pulmonary artery is the same as that in the right ventricle unless some blood from the left side of the heart is shunted into the pulmonary artery, as, for example when there is patency of the ductus arteriosus or an aortic septal defect Occasionally a high ventricular septal defect may be so located that the shunt is almost directly into the pulmonary artery Under such circumstances there may be little alteration in the oxygen content of the sample taken from the right ventricle as compared with that from the right auricle, whereas the oxygen content in the pulmonary artery may be markedly higher than that in the right ventricle The oxygen content of the blood in the pulmonary artery is of course abnormally high in patients with a complete transposition of the great vessels or with a partial transposition of the pulmonary artery

The calculations of the systemic and pulmonary blood flows offer useful information concerning the hemodynamics of the circulation and the magnitude of the various shunts For a detailed discussion the reader is referred to the works



Oxygen content expressed in Vol %
Blood pressure expressed in mm Hg

FIGURE III-3 Diagram giving the oxygen content and the blood pressure in the various chambers of the normal heart

of Cournand et al, [1] [7] Bing et al, [3] [6] Dexter et al, [4] Wood et al, [5] and others According to the Fick principle, if the oxygen content of the mixed venous blood in the right auricle and the oxygen uptake by the tissues is known, it is possible to calculate the volume of the systemic blood flow per square meter of body surface per minute Under normal conditions the volume of the systemic blood flow equals the volume of the pulmonary blood flow Thus, under basal conditions the oxygen consumption by the tissues is equal to the oxygen uptake by the lungs The oxygen uptake in the lungs is measured by the difference between the oxygen content of the blood returned from the lungs and the oxygen content of the mixed venous blood which flows to the lungs Thus the amount of the pulmonary and systemic blood flows can be expressed by the formulae [3]

$$\text{Pulmonary blood flow} = \frac{\text{Oxygen consumption}}{\text{Oxygen content of blood in pulmonary veins minus oxygen content of blood in pulmonary artery}}$$

$$\text{Systemic blood flow} = \frac{\text{Oxygen consumption}}{\text{Oxygen content of arterial blood minus oxygen content of mixed venous blood}}$$

Normally the oxygen content of mixed venous blood is the same as the oxygen content of the blood in the pulmonary artery and the oxygen content of the blood in the pulmonary veins is the same as the oxygen content in the left auricle, the left ventricle and the systemic circulation Thus, under normal conditions the systemic blood flow equals the pulmonary blood flow In the presence of a shunt this is no longer true The two may be different, either of the two may be the greater

Bing et al [3] have emphasized that the factor of vital importance to the individual is the amount of mixed venous blood which eventually becomes fully oxygenated in its passage through the lungs Bing has called this the effective flow This too can be calculated by a formula

$$\text{Effective flow} = \frac{\text{Oxygen consumption}}{\text{Oxygen content of blood in pulmonary veins minus oxygen content of mixed venous blood}}$$

As just mentioned under normal conditions these three flows are equal, but in the presence of a shunt there may be a large systemic blood flow or a tremendous pulmonary blood flow and the effective flow may be extremely meager

When any two flows are known, the various flows may be calculated as follows:

Pulmonary flow = Effective flow plus left-to-right shunt
Systemic flow = Effective flow plus right-to-left shunt
Pulmonary flow minus effective flow = Left-to-right shunt
Systemic flow minus effective flow = Right-to-left shunt
The over-all shunt = Difference between left-to-right shunt and right-to-left shunt

The volume of the systemic and pulmonary blood flows are of great importance as regards the work required of the heart. The data concerning oxygen *content of the venous blood are obtained from intracardiac catheterization.* The arterial blood should never be assumed to be fully saturated; its content should always be determined. It is, however, the effective flow which measures the oxygen supply available to the individual.

In order to compare the cardiac output of one individual with that of another, it is necessary to take into consideration the size of the individual. For this reason cardiac output is determined in relation to the surface area of the body.* The measurement of the output per square meter of body surface area is called the cardiac index. In the normal individual the minute output of the heart per square meter of body surface is approximately 2.5 to 3.0 liters, or 2500 to 3000 cc. per minute, per square meter of body surface.

Although the calculations of flows are relatively accurate for the normal individual in whom there is no shunt and in whom the difference in oxygen content between the arterial and venous blood is approximately 6 volumes per cent, this is no longer necessarily true in the presence of an arteriovenous shunt. When the arteriovenous difference is slight, any error in the determination of the oxygen content of the blood is greatly magnified. Consequently, when the oxygen content of the blood in the pulmonary artery approaches full saturation (95 to 98 per cent), and the arteriovenous difference is less than 0.5 volumes per cent, it is impossible to calculate accurately the magnitude of the shunt. Furthermore, there may be other factors at present unknown or poorly understood which alter the validity of such calculations.

*The number of square meters of body surface area is determined by the height and weight of the person. The tables for the measurement of body area are those commonly used in the determination of the basal metabolic rate. A child of 50 to 60 lbs. usually has a surface area of 1 sq. m. The surface area of an adult is approximately 1.5 to 1.7 sq. m. It is rare to find an adult with a surface area of more than [illegible] sq. m.

Oxygen consumption is determined by measurement of the basal metabolic rate.

The direct measurement of pressure is of great value It gives information concerning the pressure in the various chambers of the heart and in the great vessels and thereby offers confirmatory evidence as to where the sample was obtained, i e, from the right auricle, the right ventricle, the pulmonary artery or even from the left side of the heart

A continuous pressure tracing taken as the catheter is withdrawn from the pulmonary artery to the right ventricle or from one chamber to another, also gives valuable information

The normal mean pressure in the right auricle is approximately 1 or 2 mm of mercury whereas according to Cournand, Baldwin, and Himmelstein[27] the normal mean pressure in the left auricle is approximately 4 mm of mercury Thus *the pressure in the left auricle is normally slightly higher than that in the right auricle*

The normal pressure in the right ventricle is approximately 28/2–0 mm of mercury with a mean pressure of 7 The pressure in the right ventricle depends upon the volume of blood it is required to pump and the resistance against which it must work Thus, the pressure varies with the magnitude of the flow and the amount of resistance encountered For example, the systolic pressure in the right ventricle is elevated if the volume of the blood flow remains constant and there is obstruction at the orifice of the pulmonary artery The systolic pressure in the right ventricle may also be elevated even though the pulmonary orifice is of normal size and structure, if either the volume of the blood which enters the right ventricle is greatly increased or the pulmonary resistance is increased

The diastolic pressure in the right ventricle remains normal as long as the pulmonary valve is competent and the right ventricle empties itself completely Thus, an elevated diastolic pressure within this chamber means either the presence of pulmonary insufficiency or the failure of the right ventricle to empty itself with each ventricular contraction

The systolic pressure in the pulmonary artery is normally the same as the systolic pressure in the right ventricle, namely approximately 28 mm of mercury The pulmonary vascular bed is so large that the diastolic pressure in the pulmonary artery is normally very low approximately 7 mm of mercury Hence, the mean pressure in the pulmonary artery is in the range of 12 mm of mercury The normal pressures in the various *chambers of the heart and in the* vessels are shown in Figure III–23

The tremendous size of the pulmonary vascular bed causes the pressure in the pulmonary artery to drop very rapidly Consequently even with a large pul

monary blood flow and a high systolic pressure in the right ventricle and in the pulmonary artery, the diastolic pressure in the pulmonary artery can remain approximately normal Hickman and Cargill [8] and Riley et al [9] have estimated that the capacity of the lungs is so great that the flow of blood through the lungs must be more than three times the basal pulmonary blood flow in order to raise the pulmonary pressure Thereafter, the pulmonary pressure progressively increases The pressure in the pulmonary artery is directly proportional to the amount of blood going through the lungs and to the resistance in the pulmonary vascular bed This is a simple restatement of Poiseuille s formula that

$$\text{Pressure} = \text{Resistance} \times \text{Flow}$$

$$\text{Resistance} = \frac{\text{Pressure}}{\text{Flow}}$$

A number of factors affect the pulmonary resistance Evidence is increasing to show that there may be a neurohumoral control of the pulmonary vascular bed of such a nature as to cause vasoconstriction or vasodilatation [30] Further, the pulmonary vascular resistance is normally high at birth and drops rapidly with the expansion of the lungs An anatomical basis for these changes has been found by Civin and Edwards [31] These investigators have shown that during fetal life and at birth the smallest muscular arterioles have thick muscular walls and small lumina and that normally as the lungs expand the lumina of these vessels increase in size and the walls become thin (see Chapter iv)

In addition to the normal changes pathological changes may alter the resistance in the pulmonary vascular bed Edwards[3] has shown that when blood is ejected into the lungs under systemic pressure over a period of years there is intimal proliferation which narrows the pulmonary vascular bed and increases the resistance

Recently Arvidsson, Karnell and Moller[33] have shown that there may be multiple peripheral stenoses in the branches of the pulmonary artery which may be so severe or so numerous as to cause a significant increase in resistance to the pulmonary blood flow

When the pressure in the left auricle is elevated, it is transmitted back through the pulmonary veins to the capillaries of the lungs and if sufficiently elevated it increases the resistance to the circulation through the lungs It is quite possible that other factors not now understood may also alter the pulmonary resistance

The determination of the pressure taken when the catheter is wedged so far into the terminal branches of the pulmonary artery that fully oxygenated blood

is obtained gives an indication of the pressure in the pulmonary capillaries which in turn reflects the pressure in the pulmonary veins and the left auricle The normal pulmonary capillary pressure, or more accurately the normal wedge pressure is 4 mm of mercury, an elevation of the pressure to 12 mm of mercury or above is indicative of increased resistance Pulmonary hypertension of this nature occurs when there is obstruction to the venous return to the left side of the heart, as, for example, in mitral stenosis

If the pressure in the pulmonary artery is elevated and the wedge pressure is normal the increased pressure is due either to an increase in the volume of the pulmonary blood flow above the capacity of the lungs or to an abnormality on the arterial side of the pulmonary vascular bed or to both Thus, the abnormality of the pulmonary vascular bed may be so severe that even though the pulmonary blood flow is normal or even less than normal, the pressure in the pulmonary artery may be elevated Such a finding frequently occurs in primary pulmonary hypertension (see Chapter xviii) If on the other hand, the wedge pressure is elevated there must be some abnormality on the venous side of the pulmonary vascular bed The relative importance of these factors must always be carefully evaluated

Failure to catheterize the pulmonary artery does not necessarily mean that the pulmonary artery is abnormally placed It may arise normally from the right ventricle, but the pressure within that chamber may be so high or the pulmonary artery so small that the catheter cannot be passed into the pulmonary artery Furthermore, an abnormal current of blood may direct the catheter away from the pulmonary orifice

The left auricle may be catheterized from the right auricle when there is a gross defect in the auricular septum or when there is functional patency of the foramen ovale Passage of the catheter through the foramen ovale is relatively easy when the test is performed through the saphenous vein It is the high oxygen content of the blood in the left auricle which enables one to know that the left auricle or a pulmonary vein has been entered Pressure tracings are of aid in determining whether the catheter passed from the pulmonary vein through the left auricle to enter the right auricle or whether it passed directly from the pulmonary vein to the right auricle

The left ventricle may occasionally be catheterized by the further advancement of the catheter from the left auricle into the ventricle The systolic pressure in the left ventricle is normally the same as that in the aorta and the femoral artery As long as the aortic valve is competent and the patient is compensated the diastolic pressure in the left ventricle is approximately zero Furthermore, in

the normal individual the blood returned by the pulmonary veins to the left auricle is fully or nearly fully saturated and remains so throughout the left side of the heart Hence it is the high pressure in the left ventricle and the high oxygen content of the blood which indicate that the left ventricle has been entered

In rare instances the left superior vena cava opens into the left auricle Under such circumstances it is easy to catheterize the left ventricle by way of the left superior vena cava

Catheterization of the left ventricle directly from the right side of the heart is possible only when there is some defect in the auricular or the ventricular septum In the case of a ventricular septal defect, the flow of blood through the defect is usually from left to right, and consequently it may be difficult to pass the catheter against the stream of blood If the defect is located low in the auricular septum, as in an ostium primum defect or an ostium atrioventriculare commune defect, the catheter may readily slip from the right auricle into the left ventricle Obviously the passage of the catheter into the left side of the heart increases the information obtained from catheterization

Left heart catheterization[31-37] is now being performed through the left auricle, which can be entered directly through the left chest wall or through the left main bronchus It is a more difficult and probably a more dangerous procedure than right heart catheterization Nevertheless, it has been done with remarkable success in adults especially when the left auricle is enlarged In infants and small children the procedure is more difficult As previously mentioned, during infancy left heart catheterization can frequently be performed from the right side of the heart as the foramen ovale remains anatomically patent for several months As long as the foramen ovale is patent, if the catheterization is performed through the saphenous vein it is relatively easy to pass the catheter from the right auricle into the left auricle An experienced investigator can frequently pass a catheter from the left auricle into the left ventricle and even into the aorta

Either of the above techniques offers the possibility of studying the left side of the heart in the same manner as venous catheterization permits the study of the right side of the heart Left heart catheterization is of greatest value in patients with isolated left sided cardiac lesions especially when abnormalities of the aortic orifice are suspected This technique permits the measurement of the pressure in the left ventricle Even if the aorta is not catheterized, it is possible to compare the left ventricular pressure with the systemic pressure by determining the pressure in the femoral artery or the brachial artery and thereby to demonstrate whether or not there is an obstruction at the aortic orifice

Simultaneous catheterization of the right and left sides of the heart[34] still fur

ther increases the information obtained The more complete the physiological data obtained, the better is the understanding of the hemodynamics of the heart

Intracardiac electrocardiograms obtained by the introduction of an intra cavity electrode aid in the determination of the location of the catheter within the heart In a few instances, intracardiac electrocardiograms are of specific value For example, the point within the heart at which the change in the elec trocardiographic pattern from the auricular to the ventricular type is obtained is of diagnostic value in Ebstein s anomaly of the tricuspid valve[35] (see Chapter XXIX)

Intracardiac phonocardiography is also possible and gives information con cerning the vibrations set up within the heart This technique is another method of analyzing cardiac hemodynamics The introduction of a new procedure al ways opens up the possibility of further study and further additions to our knowledge Each new tool, however requires testing to learn its pitfalls as well as its advantages

EVALUATION OF CATHETERIZATION DATA

Cardiac catheterization is of great aid in the diagnosis of malformations when it is undertaken to obtain specific information The information gained from cardiac catheterization varies greatly with the skill of the physician who does the catheterization and with his knowledge of the physiology of the various malformations of the heart In the hands of a skilled investigator much valuable information can be obtained but when cardiac catheterization is done as a rou tine procedure without consideration of the specific problem involved the pit falls are many The ease with which the catheterization is performed greatly af fects the reliability of the various determinations For sound evaluation the samples must be truly representative of the chambers from which they are taken and the pressure tracings must be obtained simultaneously with the withdrawal of each sample It is however, dangerous to jump to conclusions when only in complete information has been obtained

In any attempt to analyze the nature of the malformation on the basis of the oxygen content of the samples of blood taken from the various places it is im portant to remember that the variations are infinite There may be one auricle or two there may or may not be a single ventricle A single auricle may occur in combination with two ventricles, or a single ventricle may be combined with two auricles Moreover the position of the tricuspid and mitral valves may be such as to produce pronounced separation of the two streams of blood as they enter a common ventricle The differentiation of an auricular septal defect from an

anomalous entrance of the pulmonary veins into the right auricle may be extremely difficult Furthermore, the flow of blood through a shunt may be such that the samples taken from the various places may even give an erroneous impression of the direction of the main shunt or even the chambers in which the shunt occurs For example, in the presence of a marked right to-left shunt a sample taken from the stream of a tiny left to-right shunt may give a false impression of the direction of the over all shunt In rare instances in the presence of an auricular defect the increase in the oxygen content of the blood may not be demonstrated in the auricular sample but may be found in the sample taken from the ventricle

Finally, it must be remembered that all the flows are calculated on the assumptions that there is a normal crossing of the two circulations and that the blood in the left auricle is fully oxygenated Neither of these assumptions is always true In patients with a large pulmonary arteriovenous fistula the oxygen saturation of the blood that is returned to the left auricle is not fully saturated in cases of complete transposition of the great vessels the formulae are not valid It must also be borne in mind that the anomalous return of one or more pulmonary veins to the right auricle is not rare, therefore, the sample of right auricular blood is not always representative of the mixed venous blood returned to that chamber

In brief the dangers are real and the pitfalls many Correct interpretation of all the information obtained is not easy Nevertheless a good catheterization may be of real aid in diagnosis

Choice of Special Procedures

When the heart is abnormally rotated or the malformation extremely complicated, an angiocardiogram prior to cardiac catheterization is of great value in demonstrating the position of the various chambers and great vessels Such knowledge helps the physician to direct the catheter properly and thereby greatly increases the chances of a successful catheterization and also lessens the risk to the patient as it eliminates needless probing of the interior of the heart

On the other hand the type of angiocardiogram which will best elucidate the malformation varies with the nature of anomaly Often, in order to obtain the full value of a special angiocardiographic technique a previous catheterization is necessary

It should, however, be remembered that special diagnostic tests are not always necessary for diagnosis or for treatment None of these tests are without

risk, and all of them are expensive Therefore none should be performed as a routine procedure for the analysis of cardiovascular defects

It is the responsibility of the cardiologist to evaluate the patient s condition and determine whether special procedures are necessary, when they should be performed, and which procedure is likely to yield the most information If more than one test appears to be necessary for accurate diagnosis, he should decide which should be done first

If the patient s condition is precarious the risk of the procedures must be evaluated Cardiac catheterization carries with it the danger of arrhythmias but it has the advantage that the procedure can be terminated at any moment, whereas in angiocardiography once the dye is injected it can be eliminated only through the kidneys For this reason the margin of safety is usually greater in cardiac catheterization than in angiocardiography

When all possible information has been obtained the final responsibility for the analysis of the data, the diagnosis of the nature of the malformation, and the treatment of the patient rests with the cardiologist

Summary

Angiocardiography aortography, and cardiac catheterization are useful adjuncts in the diagnosis of malformations of the heart Each is of greatest value when used to elucidate some specific point

Angiocardiography which is usually performed by the injection of a radio-opaque substance into the venous side of the heart demonstrates the sequential filling of the various chambers of the heart and the great vessels For this to be effective, the films must be taken in rapid succession

All such radio-opaque substances known in 1960 are toxic Deaths have occurred from their use Therefore due caution must be used in regard to the dose and the frequency of administration This technique is especially dangerous in cases of primary pulmonary hypertension and of very severe pulmonary stenosis

The technique gives good delineation of the chambers of the heart up to the point of the first major shunt

Anomalies of the superior vena cava and the right auricle are usually well demonstrated

Delineation of the ventricles gives information concerning the size of the chambers and the thickness of their walls

The visualization of the pulmonary artery from the right ventricle is normal If the aorta is visualized immediately after the right ventricle, this indicates the

presence of a shunt, either the aorta arises in whole or in part from the right ventricle or there is a shunt at the auricular level Under the latter circumstances dye will be seen in the left auricle before it appears in the aorta

Angiocardiography shows the size and position of the aorta but gives little information about the exact size of the main branches of the pulmonary artery when they are abnormally small

When coarctation of the aorta occurs as an isolated abnormality it can usually be demonstrated by angiocardiography

Selective angiocardiography means the injection of dye through a catheter placed within a specific chamber or great vessel This technique gives accurate and detailed information concerning the course of the circulation at a specific point The clinical diagnosis, however, must be relatively accurate in order to know the point at which to place the catheter in order to obtain the desired information

Cineangiocardiography offers beautiful visualization of the circulation of the blood and the action of the valves It contributes specific information, but does not give as much detail as the regular angiocardiogram, and it is difficult if not impossible to compare one film with another Thus, it has some advantages and some disadvantages

Aortography gives excellent delineation of the aorta and offers clear information concerning any shunt between the aorta and the pulmonary artery above the semilunar valves It is of great value in the demonstration of patency of the ductus arteriosus in infants before the development of the continuous murmur It may also demonstrate an aortic insufficiency or a communication between the aorta and the right side of the heart

Coronary arteriography has been perfected in order to visualize the coronary arteries and abnormalities in these vessels Its greatest use is in coronary artery diseases it also beautifully visualizes coronary arteriovenous fistulae

Further techniques will undoubtedly be developed The more specialized the technique the more accurate must be the clinical diagnosis prior to the test

Cardiac catheterization, first performed by Forssman and subsequently developed by Cournand and Richards gives information concerning the hemodynamics of the circulation If a number of samples of blood are taken and if pressure tracings are obtained from the various chambers and great vessels into which the catheter is passed, useful information can be gained concerning the location and the volume of the shunt and also concerning the relative pressures in the various chambers Hence catheterization must be done under fluoroscopic

control Monitoring the catheterization with an electrocardiogram is also essential as there is real danger of the initiation of arrhythmias and even ventricular fibrillation Because of the latter danger, a defibrillator should always be available for immediate use

Analysis of the oxygen content of the blood and of the pressures obtained in the various chambers permits estimation of the location and volume of the shunt and calculation of the systemic pulmonary, and effective flows These three flows are identical under normal basal conditions but may differ widely in various malformations

Care is needed in the interpretation of the results, not only because of possible errors in technique but also because of the location from which a sample is obtained in relation to the shunt For this reason, small shunts are difficult to evaluate Large shunts may also be difficult to evaluate if there is only a small arteriovenous difference

Left heart catheterization can be performed by direct puncture of the left auricle In adults with left auricular enlargement the procedure does not appear unduly dangerous but in young children with a left auricle of normal size, the procedure is much more difficult and may be dangerous

In infancy it is frequently possible to catheterize the left auricle through the foramen ovale if the catheterization is performed through the inferior vena cava Sometimes it is possible to advance the catheter from the left auricle into the left ventricle and thereby to catheterize all four chambers

Simultaneous left and right heart catheterization offers valuable information concerning the hemodynamics of the two sides of the heart

Intracardiac electrocardiography and phonocardiography also increase the knowledge obtained from catheterization

The amount of information obtained from cardiac catheterization varies with the skill of the operator and his knowledge of the physiology of the various cardiac malformations

When the heart is abnormally rotated angiocardiography may be desirable before cardiac catheterization is performed On the other hand the type of angiocardiogram desired depends on the type of malformation

If the patient s condition is precarious the relative risk of the procedures must be evaluated It is the clinician s responsibility to evaluate the patient s condition and to determine which procedures if any are necessary and when they should be performed it is also his responsibility to evaluate all data and to advise the patient

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Civin and Edwards in their study of normal lungs found that in early infancy the pulmonary vascular bed contains a large number of the smallest of the muscular arterioles in which the medial wall is thick and the lumen small, but the intima thin and delicate As the lungs expand, these vessels dilate, their walls become thinner and the lumina enlarge These changes normally occur rapidly after birth nevertheless the lungs continue to expand throughout infancy and indeed do not reach their maximum expansion for twenty years Edwards[1] has shown that when there is excessive pulmonary blood flow or a high ejectile force from the right ventricle the pulmonary vascular bed opens up more slowly than under normal conditions Nevertheless for several years the lung still has the potentiality for normal expansion Consequently, in the early stages these changes are considered to be reversible Over a period of years the long continued high pressure in the lungs leads to intimal proliferation Such changes are irreversible and cause progressive narrowing of the pulmonary vascular bed and ever increasing pulmonary hypertension As the pressure on the right side of the heart rises, if there is a ventricular septal defect, as soon as the pressure in the right ventricle exceeds that in the left ventricle a right to left shunt is established, if the ventricular septum is intact, no shunt will be established until the pressure in the right auricle exceeds that in the left auricle and the valve covering the foramen ovale is forced open As the right to left shunt increases, the oxygen unsaturation of the arterial blood increases, and the patient develops cyanosis Such is the commonest cause of the cyanosis and polycythemia which develop during childhood or adolescence or even during adult life

Nevertheless, Latson* has found that in young infants with a large left-to-right shunt cyanosis may be due to failure to oxygenate the blood in the lungs, as in a number of such instances he has found the blood in the pulmonary veins was not fully saturated He reports that such findings are relatively common

*Personal communication Dr Joseph R Latson

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CHAPTER IV

CYANOSIS

CYANOSIS is the bluish color of the skin which is produced by the presence of reduced hemoglobin in the circulating blood The altered color becomes visible as the blood circulates through the capillaries For this reason cyanosis is most easily seen where the capillary loops are numerous, as in the tips of the fingers and toes, the lobes of the ears, the tip of the nose, and the buccal mucous membranes The ease with which this bluish color can be detected varies with the degree of dilatation of the cutaneous capillaries and also with the thickness of the skin and its pigmentation It is a well established fact that there must be at least 5 gm of reduced hemoglobin per 100 cc of circulating blood to produce visible cyanosis Consequently, since the blood normally has a hemoglobin content of 15 gm per 100 cc, one third of the blood which circulates through the capillaries must be in the form of reduced hemoglobin to cause cyanosis

Anatomical Causes

Inasmuch as a relatively large amount of reduced hemoglobin must be present in the circulating blood for cyanosis to become apparent, cyanosis when due to a congenital malformation of the heart is indicative of a severe malformation In the vast majority of instances there is some malformation of the great vessels of such a nature that the great vessels arise from the ventricles in an abnormal manner Frequently the malformation is of such a nature that only a small volume of blood reaches the lungs and a large volume of venous blood is pumped directly into the systemic circulation In such instances the greater the reduction in the pulmonary blood flow and the greater the venous-arterial shunt, the more intense is the cyanosis When there is a complete transposition of the great vessels, the primary difficulty is not the volume of blood that reaches the lungs for oxygenation but the amount of oxygenated blood that is returned to the systemic circulation after its passage through the lungs In such instances, the greater the shunt the less is the cyanosis Secondary changes in the lungs of such a nature as to hinder the exchange of oxygen in the alveoli were formerly considered an important factor in the production of cyanosis which develops during adoles-

cence Recent physiological studies have shown that difficulty in the oxygenation of the blood in the lungs is not the usual cause of the late development of cyanosis because *in such patients, whenever it has been possible to catheterize the left* auricle, the blood in the left auricle has been found to be fully saturated

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Nevertheless, Latson* has found that in young infants with a large left-to-right shunt cyanosis may be due to failure to oxygenate the blood in the lungs, as in a number of such instances he has found the blood in the pulmonary veins was not fully saturated He reports that such findings are relatively common

Personal communication Dr Joseph R Latson

during the first year of life, are less frequently encountered during the second year of life, and rarely, if ever, occur after the third year

Further, Riley* reports that there is increasing evidence that if the lungs are not periodically properly expanded all the alveoli in the lungs are not always oxygenating the blood This phenomenon may cause a slight lowering of the oxygen saturation of the arterial blood, but this seldom occurs under normal circumstances

There are, in addition certain pathological conditions notably a pulmonary arteriovenous aneurysm or an extensive cystic disease of the lungs, in which failure of the blood to be oxygenated in its passage through the lungs is the cause of the cyanosis

Normal Physiological Considerations

RELATION OF THE OXYGEN CONTENT OF THE BLOOD TO THE AVAILABLE HEMOGLOBIN

Under normal conditions the blood which passes through the lungs is fully or nearly fully oxygenated The blood which is returned by the pulmonary veins to the left auricle is 94 to 97 per cent saturated with oxygen The fact that the arterial blood is not 100 per cent saturated has long been believed due to the fact that the bronchial veins pour some venous blood into the pulmonary veins there is, however, considerable evidence[3, 4] which indicates that the slight oxygen unsaturation may be due mainly to technical errors As the blood circulates through the capillaries approximately 22 per cent of the oxygen in the arterial blood is given off to the tissues It follows that the oxygen saturation of normal venous blood is 72 to 75 per cent Thus, normal arterial blood contains 94 to 97 per cent oxyhemoglobin and 6 to 3 per cent reduced hemoglobin and normal venous blood contains 72 to 75 per cent oxyhemoglobin and 28 to 25 per cent reduced hemoglobin

Inasmuch as 1 cc of oxygen is taken up by 0 75 gm of hemoglobin 1 gm of hemoglobin takes up 1 33 cc of oxygen, and 15 gm of hemoglobin carries 20 cc of oxygen It follows that blood with a normal hemoglobin of 15 gm per 100 cc carries 20 volumes per cent of oxygen in other words the oxygen capacity of normal blood with 15 gm of available hemoglobin per 100 cc of circulating blood is 20 volumes per cent Since the oxygen saturation of the arterial blood is 94 to 97 per cent its oxygen content is approximately 19 volumes per cent Inas-

Personal communication Dr Richard Riley

much as 22 per cent of the oxygen in the arterial blood, or approximately 5 volumes per cent, is given off in the tissues, normal venous blood has an oxygen content of 14 to 15 volumes per cent and 5 to 6 volumes per cent contains reduced hemoglobin *

Expressed in terms of grams, arterial blood normally contains slightly less than 1 gm of reduced hemoglobin, and venous blood normally contains approximately 4 gm of reduced hemoglobin The average amount of reduced hemoglobin in the capillaries is intermediate between that in the arteries and in the veins, that is, it is slightly less than 3 gm As previously mentioned, it takes 5 gm of reduced hemoglobin in the circulating blood to produce visible cyanosis It follows that in the normal individual the oxygen unsaturation of the blood circulating in the capillaries is insufficient to cause cyanosis

With exercise there is an increased demand on the part of the muscles for oxygen This is obtained by an increase in the heart rate, in the minute output of the heart, and in the circulatory rate, these increase the volume of blood which circulates through the lungs and thereby the oxygen uptake in the lungs, thus increasing the total amount of oxygenated blood supplied to the muscles With strenuous exercise more oxygen is given up in the capillaries, and there is an increase in the oxygen unsaturation of the venous blood, but not until an excessive amount of oxygen is extracted in the capillaries is there slight cyanosis

In a person with a cardiac malformation of such a nature that a varying amount of unoxygenated blood is pumped directly into the aorta the blood in *the systemic circulation is no longer fully oxygenated In an effort to increase the* supply of oxygen to the tissues there is an increase in the number of red blood cells and in the amount of available hemoglobin This, in turn, increases the amount of reduced hemoglobin in the blood and renders the cyanosis more readily apparent

*The relation of hemoglobin to oxygen

0.75 gm of hemoglobin takes up 1 cc of oxygen

1 gm of hemoglobin per 100 cc of blood take up $\frac{1}{0.75} = 1.33$ volumes per cent of oxygen

3 gm of hemoglobin per 100 cc of blood take up $\frac{3}{0.75} = 4.0$ volumes per cent of oxygen

5 gm of hemoglobin per 100 cc of blood take up $\frac{5}{0.75} = 6.7$ volumes per cent of oxygen

15 gm of hemoglobin per 100 cc of blood take up $\frac{15}{0.75} = 20$ volumes per cent of oxygen

Basic Physiological Factors in the Production of Cyanosis

Visible cyanosis, as previously mentioned depends upon an absolute amount of reduced hemoglobin in the peripheral circulation Consequently the occurrence of cyanosis depends upon the total amount of available hemoglobin and the percentage of the oxygen unsaturation of the arterial blood

CONCENTRATION OF THE AVAILABLE HEMOGLOBIN

Since there must be 5 gm of reduced hemoglobin per 100 cc of blood in the peripheral circulation to produce visible cyanosis, a patient with 15 gm of hemoglobin per 100 cc of blood will show no cyanosis until one third (33 3 per cent) of the circulating blood is in the form of reduced hemoglobin, whereas if the hemoglobin content of the blood is 20 gm per 100 cc, or 133 per cent only one-quarter of it (25 per cent) needs to be in the form of reduced hemoglobin to produce cyanosis Conversely, as the hemoglobin drops it is necessary to have a *larger percentage* of reduced hemoglobin in the circulating blood to give visible cyanosis Therefore, the height of the hemoglobin is of great importance in estimating the degree of anoxemia For example any patient who shows persistent cyanosis must have 5 gm of reduced hemoglobin per 100 cc of circulating blood This absolute amount must be subtracted from the hemoglobin determination when considering the amount of available oxygen in terms equivalent to that of a normal individual Thus if a patient with a hemoglobin of 10 gm (66 per cent) shows persistent cyanosis, he has a maximum hemoglobin of 5 gm as far as available oxygen is concerned In other words even though the hemoglobin determination is 10 gm per 100 cc of blood, the patient has a very severe anemia in terms of the oxygen content of the blood

If the anemia is severe cyanosis may entirely disappear It has been stated that if a patient had a hemoglobin of less than 5 gm (33 per cent), even though none of the blood was oxygenated there would be no cyanosis Such an example illustrates the importance of the amount of hemoglobin but is purely hypothetical since the condition would be incompatible with life Actually, as previously stated, the amount of reduced hemoglobin in the circulating blood is dependent upon two variables the total concentration of the available hemoglobin and the degree of the oxygen saturation of the arterial blood

OXYGEN SATURATION OF THE ARTERIAL BLOOD

The amount of reduced hemoglobin in the capillaries depends upon the amount of reduced hemoglobin in the arterial blood the rate of utilization of

oxygen in the capillaries, and the rate of flow of the blood Under resting conditions by far the most important factor in the production of cyanosis is the amount of reduced hemoglobin in the arterial blood This, in turn, depends upon the volume of the venous arterial shunt, the volume of blood which reaches the lungs for oxygenation and the extent of oxygenation of the blood in the lungs Thus, the oxygen content of the arterial blood is affected both by factors which operate in the systemic circulation and by factors which operate in the pulmonary circulation

FACTORS WHICH OPERATE IN THE SYSTEMIC CIRCULATION

The volume of the venous arterial shunt is an important factor in the production of cyanosis and is almost invariably operative in patients who from birth show persistent cyanosis These severe malformations are usually of such a nature that some of the blood from the right side of the heart, which is normally destined to go to the lungs for oxygenation, is pumped directly into the systemic circulation This means that a large volume of venous blood is pumped directly into the systemic circulation, and only a small volume of blood reaches the lungs for oxygenation Both factors act to increase the cyanosis

If the malformation is of such a nature that the volume of venous blood pumped into the systemic circulation results in the presence of 5 gm of reduced hemoglobin per 100 cc of blood in the *peripheral* circulation, there will be slight cyanosis This does not mean that there must be 5 gm of reduced hemoglobin per 100 cc of *arterial* blood but only that the arterial oxygen unsaturation is such that when the blood has given up its normal complement of oxygen to the tissues the oxygen unsaturation in the capillaries will be such that there are 5 gm of reduced hemoglobin per 100 cc of circulating blood This will occur when 2 to 3 gm of reduced hemoglobin are shunted into the systemic circulation Under such circumstances, as the blood circulates through the capillaries, the average amount of reduced hemoglobin in the capillaries will be increased by this amount, and consequently cyanosis will become apparent Any reduction in the oxygen saturation of the arterial blood means that there is a still further reduction in the oxygen content of the venous blood Consequently the amount of reduced hemoglobin in the venous blood is increased If the volume of the shunt is kept constant, an increase in the amount of reduced hemoglobin in the venous blood increases the amount of reduced hemoglobin shunted into the systemic circulation Cyanosis becomes progressively more intense as the amount of reduced hemoglobin in the arterial blood is increased Thus both the volume of

the shunt and the amount of reduced hemoglobin in the venous blood affects the intensity of the cyanosis In most malformations the greater the shunt, the more intense is the cyanosis

In less severe malformations in which there is adequate circulation to the lungs and slight over riding of the aorta only a small volume of venous blood with relatively normal venous saturation is pumped into the systemic circulation In such instances cyanosis is not perceptible and the oxygen unsaturation of the arterial blood can be demonstrated only by the determination of its oxygen content The occurrence of slight persistent cyanosis with a normal concentration of hemoglobin means that the oxygen saturation of arterial blood is considerably reduced usually it is between 66 and 75 per cent

The amount of blood which reaches the lungs for oxygenation is inversely proportional to the volume of the venous arterial shunt If only a small amount goes to the lungs it is inevitable that only a small volume is oxygenated When this is mixed with a large amount of unoxygenated blood cyanosis unless modified by anemia is always intense The reverse is always true if a large amount of oxygenated blood is mixed with a small amount of venous blood cyanosis is minimal For example if there is only a single ventricle and there is complete admixture of venous and arterial blood within that chamber the oxygen content of the blood directed to the lungs will be the same as that directed to the body The presence or absence of cyanosis will depend upon the amount of oxygenated blood returned from the lungs hence on the volume of the pulmonary blood flow [5]

The rate of utilization of oxygen by the peripheral tissues affects the amount of oxygen taken out of the blood as it circulates through the tissues and hence the amount of reduced hemoglobin in the capillaries Normally the increased demand of the peripheral tissues for oxygen is met by an increase in the heart rate which increases the rate of blood flow to the lungs and to the tissues

Peripheral stasis may also play a role in the production of cyanosis In a patient with persistent cyanosis and a compensatory polycythemia there are engorgement and dilatation of the capillaries and also an increase in the total number of capillaries which are open The increase in the capillary bed combined with the diminished rate of blood flow through the capillaries has a twofold effect First the dilatation of the capillaries and the increase in the number of capillaries which contain blood make the color of the blood more readily apparent and thereby lower the threshold at which cyanosis is perceptible Second the slowing of the circulation enables the tissues to take up an increased amount

of oxygen, hence, there is a greater degree of oxygen unsaturation in the venous blood and a proportional increase in the quantity of reduced hemoglobin in the capillaries

FACTORS WHICH OPERATE IN THE PULMONARY CIRCULATION

Although under normal conditions the blood which passes through the lungs is fully or nearly fully oxygenated, there are a number of factors which may alter the extent of the oxygenation of the blood in its passage through the lungs Some are physiological, some due to disease, and some due to changes in the pulmonary vascular bed Physiological changes and those caused by pulmonary disease, although of great importance, are beyond the scope of this book hence, these factors are only briefly mentioned For a detailed discussion the reader is referred to the various authorities[6 8] in this field

The vital capacity of the patient is obviously important A fall in the vital capacity lessens the exchange of oxygen and carbon dioxide in the lungs

The rate of blood flow through the lungs also affects the volume of blood oxygenated in the lungs With an increase in heart rate and an increase in the minute output, the increased rate of blood flow through the lungs increases the rate of oxygen uptake and hence the amount of oxygen which is supplied to the body Occasionally with severe exercise, the rate of the circulation through the lungs may be so rapid that in spite of maximum ventilation there is no longer time for complete oxygenation of the blood This may be a potent factor in the production of the cyanosis which occasionally occurs in the normal individual upon strenuous exercise In a patient with pulmonary stenosis and a venous arterial shunt, the cyanosis which occurs with exercise has a quite different origin The pulmonary stenosis prevents the normal increase in the pulmonary blood flow and consequently the increase in cardiac output which occurs with exercise instead of causing an increase in the pulmonary blood flow causes an increase in the venous arterial shunt, which in turn causes a fall in the oxygen saturation of the arterial blood

Partial pressure of the oxygen in the inspired air affects the rate of diffusion of oxygen through the pulmonary alveoli For this reason the reduction in the partial pressure of the oxygen which occurs at high altitudes produces cyanosis This factor is even more vitally important to patients whose cardiac condition causes some degree of oxygen unsaturation than it is to normal individuals The fact that infants with severe malformations of the heart may be born, live, and die at high altitudes does not mean that altitude has no effect upon the oxygen

saturation of the arterial blood *Altitude appears to be unimportant only be cause this factor is constant throughout the life of the individual* Nevertheless a malformation which is incompatible with life at a high altitude may be compatible with life at sea level Conversely, because an infant with persistent cyanosis can live at sea level, it does not mean that he will be able to adjust to or necessarily survive the reduction in the partial pressure of the oxygen which occurs at high altitudes Without exception all patients who show persistent cyanosis will suffer a further increase in arterial unsaturation as the partial pressure of the oxygen is reduced Therefore, high altitudes and air travel without supplementary oxygen are contraindicated

The concentration of the blood is also important The number of red blood cells per cubic millimeter of blood may be so great that in all probability the red blood cells no longer pass through the pulmonary capillaries in single file All recent experimental evidence indicates that this is not a factor of great importance in the oxygenation of the blood

Pulmonary diseases such as pneumonia, advanced tuberculosis actinomycosis extensive cystic disease of the lungs, and in some instances extreme pulmonary sclerosis or endarteritis cause cyanosis

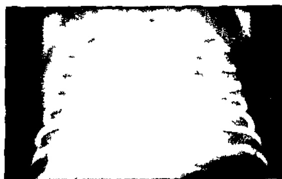
Failure of the blood to be oxygenated as it passes through the lungs was emphasized by Lundsgaard and Van Slyke[6] in their classic studies on cyanosis as a factor of great importance in patients with polycythemia They showed that in most patients with marked polycythemia, the oxygen saturation of the arterial blood could be markedly elevated by the prolonged inhalation of 100 per cent oxygen This observation can be readily confirmed Recent physiological studies however, have shown that in patients with a marked polycythemia in whom the inhalation of oxygen lessens the cyanosis, whenever it has been possible to catheterize the left auricle the blood in the pulmonary veins has been found to be fully saturated For this reason it seems that in many instances the inhalation of oxygen may alter some nervous or neurohumoral mechanism[7] in the lungs, and thereby alter the volume of the pulmonary blood flow rather than the permeability of the capillaries Indeed the effect of the inhalation of oxygen on the pulmonary blood flow is now (in 1960) used as a method to determine the flexibility of the pulmonary vascular bed (see Chapter xxiv)

The deposit of hyaline material as a membrane in the alveolar ducts is a common cause of cyanosis during the first three days of life in premature babies and in babies of diabetic mothers These babies suffer from severe respiratory distress and increasing cyanosis X ray reveals diffuse fine stippling throughout the



C y of D Clem t t Sm h B Ly g I H p t l

Moderate degree in a slightly premature infant



C t sy f D Cl m A Sm h B Ly g l H p t l

Severe degree in a small premature infant one hour after birth

FIGURE IV–1 Hyaline membrane Infant

lungs, as shown in the upper x ray of Figure IV–1 Some babies with these changes recover with no apparent residual abnormality Usually however, the condition progresses to a fatal termination When the condition is severe the shadows coalesce leaving the air filled bronchial tree sharply outlined (see lower x ray of Figure IV–1) Autopsy in such instances shows a hyaline membrane lining the alveolar ducts

Congenital anomalies in the pulmonary vascular bed as, for example, a pulmonary arteriovenous aneurysm (see Chapter XVI), may be a potent factor in the production of cyanosis Extensive cystic disease in the lungs may alter the permeability of the alveoli to such an extent that the patient develops intense cyanosis under such circumstances the inhalation of oxygen causes the prompt disappearance of the cyanosis

Broadly speaking, there are three main abnormalities which lead to the production of cyanosis The first is inadequate circulation to the lungs, the second is difficulty in the return of oxygenated blood to the systemic circulation, and the third is failure of the blood to be fully oxygenated in its passage through the lungs

Inadequate circulation to the lungs combined with a venous-arterial shunt is the cause of cyanosis in a tetralogy of Fallot The greater the reduction in the circulation to the lungs, the greater is the venous arterial shunt The importance of the reduction in the pulmonary blood flow in the production of cyanosis has been clearly illustrated by the Blalock Taussig operation in which a marked increase in the oxygen saturation of the arterial blood occurs upon increasing the volume of mixed venous blood directed to the lungs Indeed, in all malformations in which there is pulmonary stenosis and in which the aorta receives some venous blood from the right side of the heart even though the defect within the heart remains unchanged, an increase in the volume of venous blood which reaches the lungs immediately lessens cyanosis

Difficulty in the return of the oxygenated blood to the systemic circulation is the primary cause of cyanosis when there is a complete transposition of the great vessels Under such circumstances plenty of blood reaches the lungs for oxygenation, and a large volume of oxygenated blood is returned to the left auricle and the left ventricle Nevertheless, inasmuch as the pulmonary artery arises from the left ventricle, most of the blood is pumped directly from the left ventricle into the pulmonary artery and re-circulates through the lungs (see Chapter x) Under such circumstances, it is difficult for oxygenated blood to reach the systemic circulation and for venous blood to reach the lungs

Failure of the blood to be fully oxygenated in its passage through the lungs occasionally occurs in young infants with a large left to right shunt, and may also occur in older persons during prolonged shallow breathing Furthermore it occurs in patients with arteriovenous aneurysms or with cystic diseases of the lung

Pulmonary vascular changes were formerly believed to hinder the oxygenation of the blood in the lungs Recent physiological studies indicate that the pulmonary vascular changes per se do not alter the permeability of the alveolar capillaries but lead to intimal proliferation which increases the resistance in the pulmonary vascular bed and thereby increases the pressure against which the right ventricle must work As the pulmonary vessels become progressively narrower, the pulmonary resistance steadily increases When the pressure in the

right ventricle equals or slightly exceeds that in the left ventricle, if there is a communication between the two sides of the heart, a right to left shunt is established Thereafter the further constriction of the pulmonary vascular bed increases the right to left shunt Such is the most usual cause of the cyanosis which develops during childhood or adolescence

The above analysis indicates that reduction of the volume of venous blood reaching the lungs or failure of oxygenated blood to be directed to the systemic circulation is the usual cause of cyanosis in infancy and that alteration in the pulmonary vascular resistance combined with an intracardiac shunt is the principal factor operative in the development of cyanosis in later life

Methods for the Determination of the Cause of Cyanosis

X RAY EVIDENCE

The size of the pulmonary artery as visualized in the x ray gives an important clue to the volume of blood which reaches the lungs Absence of fullness of the pulmonary conus means that the pulmonary artery is diminutive, absent, or misplaced If it is diminutive or absent the main branches of the pulmonary artery are small and the hilar shadows are quiet If, on the other hand, there are large blotchy hilar shadows which upon fluoroscopy may show pronounced pulsations it means that the pulmonary arteries are large and that the pulmonary blood flow is excessive This finding when combined with a concave curve at the base of the heart to the left of the sternum, is indicative of a posteriorly placed pulmonary artery and hence of a complete transposition of the great vessels

On the other hand, fullness of the pulmonary conus usually means that the pulmonary artery arises in its normal position Under such circumstances the main branches of the pulmonary artery are usually readily seen In patients with pure pulmonary stenosis there may be conspicuous pulsations of the pulmonary conus but minimal pulsations in the branches of the pulmonary artery whereas in patients with excessive pulmonary blood flow there is generally a definite hilar dance In the presence of fullness of the pulmonary conus and a hilar dance cyanosis, if present, is due to a venous-arterial shunt at either the auricular or ventricular level, to an over riding or transposed aorta or in rare instances to a pulmonary arteriovenous aneurysm The hilar dance indicates excessive pulmonary blood flow and may indicate increased pulmonary pressure Occasionally, a transposed aorta arises so far to the left that it occupies the posi

tion of the normal pulmonary artery Under such circumstances, although there is fullness of the pulmonary conus, the lungs usually appear disproportionately clear

PHYSIOLOGICAL TESTS

Cardiac catheterization has contributed more to the understanding of the physiology of malformations of the heart than any other single procedure By cardiac catheterization information is obtained concerning the location, direction, and volume of the shunt or shunts and concerning the pressures in the various chambers and vessels into which the catheter is passed This technique and the information derived from it are discussed in detail in Chapter III The following discussion is concerned with the simpler tests which are of aid in the detection of venous-arterial shunts

The red blood cell count, the *level of the available hemoglobin* and the *hematocrit reading* are of diagnostic value When the oxygen saturation of arterial blood is below 66 per cent or falls below this level with exercise polycythemia develops As polycythemia increases the oxygen saturation of the arterial blood rises, so that in older patients with deep persistent cyanosis the oxygen saturation of the arterial blood is frequently between 78 and 88 per cent, whereas in the absence of polycythemia this degree of arterial unsaturation does not produce visible cyanosis but usually causes a slight elevation in the red blood cell count and in the level of the available hemoglobin

In infants and young children the finding of a slightly elevated or even normal red blood cell count and hemoglobin level at a time when anemia is physiological should suggest the possibility that the arterial blood is not fully saturated

The determination of the oxygen saturation of the arterial blood demonstrates the presence of reduced hemoglobin in the circulating blood which is insufficient to cause visible cyanosis Furthermore, when there is cyanosis the degree of oxygen unsaturation of the arterial blood is important It is difficult to estimate clinically the severity of the oxygen unsaturation, partly because variations in the intensity of the cyanosis are not easy to determine and partly because the intensity of the cyanosis varies with the amount of available hemoglobin and the height of the red blood cell count

The oxygen saturation of the arterial blood in infants with malformations of the heart which cause persistent cyanosis is frequently extraordinarily low An oxygen saturation of the arterial blood of 30 per cent obtained from a cyanotic infant when he is crying is not unusual and generally not dangerously low Such

a saturation is, however, seriously low if obtained under basal or nearly basal conditions An arterial oxygen saturation of under 20 per cent is always cause for concern and one of 10 per cent or less is of grave prognostic import Those who are unaware of how low the oxygen content of the arterial blood may be frequently assume that because the saturation is far lower than expected, the blood must have been taken from a vein and not from an artery Such an assumption is a serious mistake On the contrary it should always be remembered that if the oxygen content of the femoral vein is extremely low, that of the arterial blood cannot be very much higher

Although under normal conditions the arterial oxygen saturation is the same in both the upper and lower extremities, in a few malformations it makes a profound difference from what artery the sample of blood is drawn There are two conditions in which the blood in the brachial artery can show full saturation and that in the femoral artery definite unsaturation The first occurs in an infant with a complete interruption of the isthmus of the aorta, and the second occurs in a patient with marked pulmonary hypertension and persistent patency of the ductus arteriosus in whom the flow of blood is from the pulmonary artery through the ductus arteriosus into the descending aorta

The effect of exercise upon the oxygen saturation of the arterial blood offers important evidence as to the nature and the severity of the malformation In patients with pulmonary stenosis and an aorta which arises in part or entirely from the right ventricle, exercise causes a marked reduction in the oxygen saturation of the arterial blood This is so uniformly true that if a patient shows minimal or no cyanosis, a simple exercise test and observation of changes in the patient s color give sufficient information to determine whether cyanosis is due to peripheral stasis or a severe cardiac abnormality Thus this test may eliminate the necessity for the determination of the oxygen content of the arterial blood

The effect of the inhalation of oxygen upon the oxygen saturation of the arterial blood depends upon the volume of venous blood shunted into the systemic circulation and the ability of the blood to take up oxygen in its passage through the lungs The prolonged inhalation of oxygen can never alter the oxygen unsaturation which results from the direct shunting of venous blood from the right ventricle into the systemic circulation but it may markedly lessen the unsaturation due to pulmonary factors Therefore this simple test gives information as to the relative importance of systemic and pulmonary factors but does not indicate the nature of the pulmonary factors

Recent physiological studies have shown that in most malformations including those in which there is pulmonary hypertension the blood returned to the

left auricle is usually fully saturated These observations clearly indicate that the oxygenation of the blood in the lungs is generally normal Therefore, the benefit derived from the inhalation of oxygen must be through its influence on the volume of blood directed to the lungs, this in turn suggests the existence of some nervous control over the volume of the pulmonary blood flow Certain it is that the changes in the oxygen saturation of the arterial blood associated with the inhalation of oxygen should not be assumed to offer a simple means for measuring the volume of the pulmonary blood flow or be used as proof that cyanosis is due to the failure of blood to be completely oxygenated in its passage through the lungs

CIRCULATION TIME

Determination of the circulation time is a simple and useful test When there is a right to-left shunt the circulation time is usually markedly shortened For example if the aorta over rides the right ventricle some blood from the right ventricle is pumped directly into the systemic circulation Therefore the circulation time from the arm to the systemic circulation is abnormally short Such a finding does not mean that the circulation of the blood through the systemic circulation is unusually rapid, it merely demonstrates the existence of a right to-left shunt

Various tests have been devised to study the circulation time Most of these methods start with the injection of some material into the vein that is, they start on the venous side

The pulmonary circulation time may be measured by the injection of ether into the vein The interval between the injection of ether and its detection on the patient s breath indicates the pulmonary circulation time In reality the circulation time is much shorter than this Ether must not only reach the lungs, it must be exhaled by the patient inhaled by the operator, and then the reaction recorded In contrast to the seven to ten seconds required for the observer to record the circulation time visualization of the pulmonary vessels by angiocardiography normally occurs in a second or two after the injection of the dye In cases of a venous arterial shunt the injection of ether into the systemic circulation may cause a serious reaction The patient usually complains of a severe headache hemiplegia and even sudden death have resulted from this procedure For this reason the dose must be low 1 drop of ether in 3 cc of normal saline solution is usually adequate Actually it is seldom necessary to measure the pulmonary circulation time

The systemic circulation time is measured by the injection of some type of

test material into a vein, this material circulates through the lungs and is returned to the left side of the heart and thence to the systemic circulation When so measured the normal circulation time is twelve to twenty seconds, depending upon the heart rate and the rapidity with which the material is injected The more rapid the heart rate, the shorter is the circulation time On the other hand the systemic circulation time is markedly prolonged in patients with cardiac failure

A marked shortening of the systemic circulation time occurs whenever a sufficient quantity of test material passes directly from the right side of the heart into the systemic circulation without passing through the lungs It follows that an abnormally short circulation time is an indication of a venous arterial shunt instead of the usual twelve to twenty seconds the circulation time will be three to five seconds, or even less

Various substances may be used to measure the systemic circulation time

Saccharine (2 to 4 cc of a 50 per cent solution) produces a sweet taste in the mouth [9] The time when it is first noted measures the circulation time from the arm to the tongue

Decholin (2 to 3 cc of a 20 per cent solution) also gives the circulation time from the arm to the tongue [10] It is a safe method but requires a certain amount of cooperation on the part of the patient Although a young child may fail to speak when he first tastes the salt, his facial expression usually reflects the unpleasant taste

Fluorescein (0 5 to 2 cc of a 20 per cent solution) or *Riboflavin* (0 8 mgm per kg of body weight), when injected into the circulation can be detected by its yellow color as it circulates through the body [11] This color can readily be seen when the patient is viewed in a darkened room beneath a mercury vapor lamp The circulation time is usually measured by the time required for the dye to reach the lips and tongue because the color is easily seen in the buccal mucous membranes This test has the great advantage of being a simple objective test It occasionally causes nausea but seldom causes any serious untoward reactions

Calcium gluconate (3 cc of a 10 per cent solution), when injected rapidly causes a tingling sensation in the limbs [1] This simple test gives an indication of the rate of circulation to the various parts of the body but requires the cooperation of the patient

The use of the circulation time to estimate the volume of the shunt has been suggested by Prinzmetal [12] In a patient with a venous arterial shunt the shortened circulation is demonstrated only provided a sufficient amount of test ma

terial is passed directly through the shunt to give a prompt reaction Therefore by starting with a small dose and gradually increasing the dose, a point will be reached at which an abrupt shortening of the circulation time will occur The smaller the dose required to reach this level, the larger is the volume of the venous arterial shunt Such tests are safe with decholin or saccharine but should never be attempted with any material which is excreted slowly

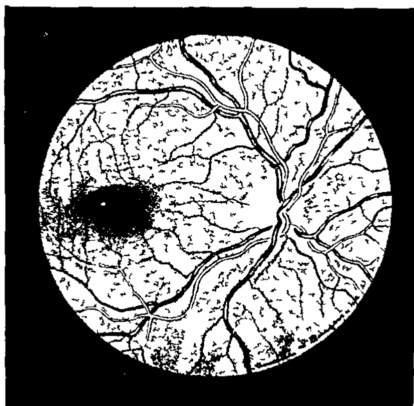
In the author s experience this test has not given reliable results Indeed, the method is of little value in infants or children because the normal circulation time is much shorter than in adults At times it may be difficult to determine whether the short circulation time is due to a shunt or merely to the rapidity of the heart rate Cardiac catheterization gives so much more information concerning the volume of the shunt that the above mentioned method is seldom utilized

Clinical Manifestations

The appearance of the patient is characteristic The individual has a dusky ruddy complexion Delayed closure of the fontanelles and frontal bossing is common when polycythemia develops early This may be so extreme that the infant or young child looks as if he had hydrocephalus The occurrence of cyanosis and clubbing of the extremities however, immediately suggests that the condition is due to a congenital malformation of the heart

Cyanosis caused by a cardiac malformation always precedes clubbing When cyanosis is not pronounced it is most readily observed in the buccal mucous membranes and the pharyngeal wall, which are of a deep mulberry color Usually there is suffusion of the conjunctivae Examination of the eye grounds reveals dilatation and congestion of the retinal vessels (see Figure IV–2) The capillaries throughout the body become dilated This is readily apparent beneath a capillary microscope Everywhere on the surface of the body the capillaries are seen to be far more numerous and the number of red blood cells in the individual capillaries is increased Nevertheless in infants cyanosis is often difficult to see and it is surprising how severe the malformation of the heart may be without the development of conspicuous cyanosis

The age at which cyanosis appears gives a clue to its origin Cyanosis due to the direct shunting of venous blood from the right ventricle into the aorta usually is apparent in infancy Occasionally if the foramen ovale is widely patent and there is extreme pulmonary stenosis cyanosis may date from birth If however the shunt is through a foramen ovale which is held open by the high pres-



[illegible]

FIGURE IX–2 Changes in the eye ground due to polycythemia in a patient with a congenital malformation of the heart From a colored drawing by Annette Burgess

sure in the right auricle, cyanosis generally develops insidiously between two and seven years of age Even if it is present at birth, it usually disappears and does not recur until the patient is a year and a half or two years of age

Cyanosis which develops at puberty or in early adult life is usually due to secondary changes in the lungs It is however, not due to inability to oxygenate the blood in the lungs The secondary changes in the pulmonary vascular bed are of such a nature as to cause progressive narrowing of the small muscular arteries and ever increasing pulmonary hypertension The cyanosis is due to the development of or an increase in the right to-left shunt which results from the increased resistance in the pulmonary vascular bed Even in patients with severe pulmonary hypertension, cyanosis occurs only when there is a right to-left shunt If there is a ventricular septal defect, blood is shunted from the right ventricle into the aorta If the ventricular septum is intact, the increased pressure in the right

ventricle sooner or later elevates the pressure in the right auricle Then, if the foramen ovale is not completely sealed, the valve is forced open and a right-to-left shunt established at the auricular level

The distribution of the cyanosis should be observed with care When the pressure in the pulmonary artery is greater than that in the descending aorta and the ductus arteriosus is patent, blood flows from the pulmonary artery to the descending aorta

When this occurs the head and the upper extremities receive well-oxygenated blood from the ascending aorta and the trunk and the lower extremities receive a mixture of arterial blood from the aorta and venous blood from the pulmonary artery Consequently the head and the upper extremities are of normal color and the lower extremities are cyanotic If the pressure in the ascending aorta is lower than that in the pulmonary artery some venous blood is forced back into the left subclavian artery Under such circumstances the left hand is more cyanotic than the right hand If the condition is marked it gives the impression of a longitudinal distribution of the cyanosis of the chest and thorax In reality the left hand and both feet are cyanotic Furthermore if the back is examined with care it will be found that the top of the shoulders are of normal color and the remainder of the thorax and trunk are cyanotic The line of demarcation of the cyanosis posteriorly lies across the shoulders and extends slightly lower down on the right shoulder than on the left (see Chapter XVIII) Frequently when the cyanosis is less intense the difference in cyanosis between the two hands may not be obvious and that between the left hand and the feet may be slight but a comparison of the right hand and the feet will show a definite difference in color

In patients with complete transposition of the great vessels the pulmonary artery arises from the left ventricle and carries oxygenated blood Consequently whenever the ductus arteriosus is patent and blood flows from the pulmonary artery to the descending aorta oxygenated blood is carried to the lower extremities (see Chapter X) Under such circumstances the difference in the cyanosis of the hands and the feet is reversed the upper extremities are more cyanotic than the lower extremities Owing to the fact that in complete transposition of the great vessels the pressure in the two circulations is approximately equal there is no back pressure of arterial blood into the left subclavian artery Since the skin of the trunk and abdomen receives its nutrition through the small branches of the subscapular arteries the internal mammary arteries and the superficial epigastric arteries all of which arise from the aorta above the en

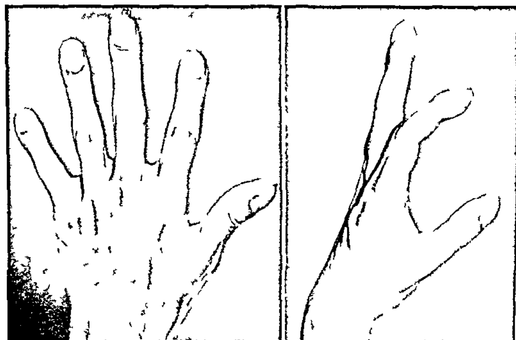


Figure iv–3 Clubbed fingers

trance of the ductus arteriosus, the line of demarcation of the cyanosis lies at the brim of the pelvis

The hands are frequently more cyanotic than the feet in children with marked polycythemia This is probably due to the fact that the children use their hands more than their feet Hence there is greater deoxygenation in the peripheral tissues of the hands than of the feet In such patients the hands show intense cyanosis which gradually diminishes over the forearm, but there is no line of demarcation of the cyanosis between the upper and the lower extremities

Clubbing of the fingers and toes is an outstanding feature in older patients with severe congenital malformations of the heart of such a nature that there is a persistent venous-arterial shunt The terminal phalanges become bulbous, and there is a longitudinal curvature of the nails (see Figure iv–3) These changes, however, take time to develop

Clubbing is never present at birth and is rarely seen during the first months of life The initial changes are due to dilatation and engorgement of the capillaries associated with polycythemia In infancy the development of a severe anemia which increases the ... but lessens the polycythemia may cause the disappearance of ... *in one infant the clubbing of the*

fingers and toes (the most pronounced the author has ever seen at one year of age) completely disappeared upon the development of a secondary anemia due to a terminal infection This observation shows that in infancy the presence or absence of clubbing is not an index of the duration of the cyanosis but of the de gree of the polycythemia The importance of the dilatation of the capillaries is demonstrated by the fact that a patient with pulmonary hypertension and re versal of blood flow through the ductus arteriosus may show not only cyanosis of the left hand but also clubbing of the fingers of that hand The red blood cell count is uniform throughout the body but the capillaries in the left hand be come engorged and dilated

In older persons the absence of clubbing is significant It indicates either that the polycythemia has always been slight or that it has only recently occurred In tense cyanosis without clubbing after the age of two indicates that the cyanosis has been of short duration It is suggestive either of a reversal in the direction of the shunt or of the development of some acute pulmonary pathology Clubbing due to a congenital malformation of the heart without cyanosis rarely if ever occurs Indeed it is seen only immediately after a rapid fall in the hemoglobin For example after a successful Blalock Taussig operation, cyanosis promptly disappears and over a period of months clubbing regresses and may eventually disappear If clubbing is present without cyanosis some other explanation for the clubbing should be sought as for example a lung abscess Clubbing and cyano sis when they occur together are always suggestive of a severe malformation of the heart

Polycythemia develops to compensate for anoxemia Patients with threshold cyanosis and an oxygen saturation of the arterial blood of 66 per cent to 75 per cent who can maintain this level upon exercise seldom develop polycythemia Infants may have an extraordinarily low oxygen content of the arterial blood be fore they develop clubbing or polycythemia Nevertheless it appears that the persistence of an arterial oxygen saturation below 66 per cent over a period of time leads to the development of polycythemia and of collateral circulation Fur thermore in the author s experience there is some evidence which suggests that arterial oxygen unsaturation to the trunk and lower extremities leads to the de velopment of polycythemia but when the arterial unsaturation is limited to the head and upper extremities this stimulus is not present This observation how ever requires further study before any importance should be attached to it

Polycythemia may be present from early infancy but usually develops during early childhood The red blood cell count is frequently 6 to 8 million per cu mm

and may reach 10 million and occasionally 12 million, but seldom goes higher than that There is a proportional increase in the concentration of the hemoglobin and in the level of the hematocrit The hemoglobin is usually above 100 per cent and may be over 140 per cent The hematocrit reading (the volume of packed red blood cells per 100 cc of blood) may reach 80 and occasionally 90 The high hematocrit is almost entirely due to the increase in the number of the red blood cells, the white blood cell count remains unchanged

The spleen contrary to cases of polycythemia vera is not enlarged

Factors which Affect Cyanosis

FACTORS WHICH LESSEN CYANOSIS IN THE NEONATAL PERIOD

The ductus arteriosus is normally patent at birth and often acts in a compensatory manner In virtually all malformations in which there is obstruction in the pulmonary circulation and the pulmonary pressure is low, blood flows from the aorta through the ductus arteriosus to the lungs Therefore, in cases of pulmonary stenosis or atresia associated with a venous arterial shunt, so long as the ductus arteriosus remains patent, this pathway increases the volume of venous blood which reaches the lungs for oxygenation, and thus lessens the cyanosis

The hemoglobin is normally high at birth and immediately thereafter drops rapidly Although in an infant with persistent cyanosis the fall in the hemoglobin may not be as abrupt and may not reach as low a level as in a normal individual, any decrease in the hemoglobin lessens the intensity of the cyanosis

Atelectasis often occurs during the first days of life and may be the sole cause of cyanosis With the complete expansion of the lungs such cyanosis disappears When present in an infant with a severe malformation, atelectasis increases the intensity of the cyanosis Cyanosis due to atelectasis can be differentiated from that due to a congenital malformation of the heart by the degree of cyanosis induced by crying If the cyanosis is due to atelectasis, it is decreased by crying, if it is due to a congenital malformation of the heart, crying intensifies the dusky hue The development of, or an increase in the intensity of the cyanosis upon nursing or crying is a common phenomenon However, it is due not to a shunt reversal but to an increase in the venous-arterial shunt in which, at rest, the quantity of reduced hemoglobin is insufficient or barely sufficient to produce cyanosis

In brief immediately after birth the various factors concerned with the production of cyanosis usually operate in such a manner as to lessen cyanosis during

the neonatal period In early infancy it is not easy to detect cyanosis unless it is very intense Even if there is intense cyanosis at birth the cyanosis frequently lessens during the neonatal period Occasionally it may entirely disappear

FACTORS WHICH CAUSE DISAPPEARANCE OF CYANOSIS

There are a few malformations which may cause extreme cyanosis in the early months of life but in which the cyanosis is not persistent Persistence of cyanosis is commonly attributed to the failure of the valve covering the foramen ovale to close Such is the cause of cyanosis only if the pressure in the right auricle is abnormally high Indeed only so long as the pressure in the right auricle is greater than that in the left auricle is there a right to-left shunt With the expansion of the lungs and the fall in pressure in the lesser circulation, blood is directed to the lungs, all the blood from the lungs is returned to the left auricle Just as soon as the pressure in the left auricle exceeds that in the right auricle the valve which covers the foramen ovale even though not completely sealed is functionally closed and there is no longer any admixture of venous and arterial blood Thus, under normal circumstances a balance between the two sides of the heart is promptly established usually within the first few cardiac cycles of extra uterine life

In the author s experience, infants who have shown intense cyanosis during the first months of life and in whom the cyanosis has gradually disappeared have had some severe malformation of the heart Such may be the course of events in a patient with a large defect in the auricular septum A similar sequence of events may occur in a patient with valvular pulmonary stenosis and an intact ventricular septum A patient with the former malformation will remain acyanotic whereas one with the latter abnormality will usually again develop cyanosis during childhood Cyanosis of this origin generally recurs insidiously between two and seven years of age and thereafter becomes persistent

Although slight lessening of cyanosis in the neonatal period is common, unfortunately the disappearance of cyanosis is rare The improvement is usually but temporary within a few weeks the cyanosis reappears and thereafter becomes progressively more intense

FACTORS WHICH INCREASE CYANOSIS

An infant who shows no cyanosis in the neonatal period may show cyanosis when he nurses or cries and later develop intense cyanosis

The development of cyanosis during infancy is usually due to structural

changes which take place after birth After the establishment of the pulmonary circulation, the pulmonary pressure rises, and less blood flows through the ductus arteriosus to the lungs During the ensuing weeks or months, the ductus arteriosus undergoes obliteration In many malformations the obliteration of the ductus arteriosus decreases the volume of blood which reaches the lungs to such an extent that the condition becomes incompatible with life In some instances the hemoglobin which drops abruptly in the neonatal period, tends to rise, thereby rendering cyanosis more and more readily apparent In other instances cyanosis does not become apparent until the infant starts to walk During the first year the later the appearance of cyanosis, the less severe is the malformation In still other instances cyanosis may not become apparent until childhood or even adolescence

Cyanosis frequently develops during childhood in patients with isolated right sided cardiac lesions in whom the foramen ovale has not become completely sealed Under such circumstances as the pressure in the right ventricle rises, the pressure in the right auricle is also increased When the pressure in the right auricle exceeds that in the left auricle the valve covering the foramen ovale is forced open and a right to-left shunt is established Such is the origin of the cyanosis in valvular pulmonary stenosis with an intact ventricular septum, in Ebstein s anomaly of the tricuspid valve, and also in primary pulmonary hypertension

Cyanosis usually becomes visible during adolescence in patients with an Eisenmenger complex, that is, a ventricular septal defect with increased pulmonary blood flow and high pulmonary pressure Indeed, it is the ejection of blood into the lungs under high pressure which causes intimal proliferation of the very small pulmonary arterioles, this in turn increases the resistance in the lungs Thus a vicious cycle is set up The pulmonary hypertension increases the pressure against which the right ventricle must work and consequently the pressure in that chamber is still further increased and this in turn still further injures the lungs Under such circumstances a septal defect acts as an escape valve and permits the establishment of and the gradual increase in the volume of the right to-left shunt Cyanosis of this origin is of grave prognostic import because it is indicative of severe and progressive injury to the pulmonary vascular bed

DURATION OF CYANOSIS

Knowledge of the duration of the cyanosis is important in order to differentiate cyanosis which is due to a temporary reversal in the direction of the shunt

from cyanosis which results from a persistent right to left shunt A clue to the duration of the cyanosis can be obtained from the rate of growth of the infant Although at birth an infant with a serious malformation of the heart may be of normal size, persistent anoxemia causes stunting of extra uterine growth This phenomenon is so constant that if the growth of the infant has been normal it is evidence that severe anoxemia has not been present throughout life

In older children the presence or absence of clubbing and polycythemia offers valuable information The anoxemia associated with persistent cyanosis leads to polycythemia and clubbing of the fingers and toes Intense cyanosis due to a reversal in the direction of the shunt causes no immediate increase in the number of the red blood cells nor does it produce clubbing Cyanosis appears before clubbing, therefore when cyanosis develops late in life there is a discrepancy between the intensity of the cyanosis and the degree of the clubbing In these individuals after the appearance of cyanosis the duration of life may be so limited that this discrepancy is never overcome

COMPLICATIONS SECONDARY TO PERSISTENT CYANOSIS

The outstanding complications which occur in patients with persistent cyanosis are due to anoxemia and polycythemia The following discussion is concerned with the physiology of these complications Their treatment is discussed in the chapter on medical care

Anoxemia in infants is usually far more severe than is indicated by the intensity of the cyanosis Indeed many infants die from lack of oxygen before the development of polycythemia, and consequently without intense cyanosis In an infant with a tetralogy of Fallot it is not unusual to find an arterial oxygen saturation of 30 per cent and in those with a complete transposition of the great vessels it may be far lower The author has seen one infant in whom the oxygen saturation of the arterial blood was less than 1 per cent the day before death Needless to say severe anoxemia is an indication for surgery if it is possible (see Chapter VI)

Fever may be caused by anoxemia when it is severe and of long duration

Attacks of paroxysmal dyspnea are common in infants with a venous arterial shunt and severe pulmonary stenosis or pulmonary atresia and occasionally occur in infants with a pseudo truncus arteriosus

These attacks appear to be associated with a reduction in the pulmonary blood flow They occur most frequently at the time the ductus arteriosus is undergoing obliteration It seems as though during the process of obliteration the

ductus arteriosus periodically clamps down and then opens up This impression is based upon the fact that the author has seen several infants with pseudo truncus arteriosus who suffered from attacks of paroxysmal dyspnea during which the continuous murmur disappeared (see Chapter xiv) In those patients the attacks of paroxysmal dyspnea were clearly related to a sharp reduction in the pulmonary blood flow and a consequent abrupt fall in the oxygen saturation of the arterial blood

Furthermore during the attacks of paroxysmal dyspnea the oxygen saturation of the arterial blood may drop to an extremely low level In most instances when a sample of blood is obtained during an attack, the oxygen saturation of the arterial blood is between 8 and 14 per cent When the arterial oxygen saturation falls abruptly to less than 10 per cent infants generally suffer from loss of consciousness Most of these infants get their breath better in the knee-chest position Many of them prefer to sleep in this position The treatment of attacks of paroxysmal dyspnea is discussed on pages 170–171

Dyspnea is the result of cerebral anoxia Under normal conditions the oxygen supply to the body is regulated by the rate of oxygen uptake in the lungs Normally with exercise there is an increase in heart rate, an increase in the rate of the pulmonary blood flow, and a corresponding increase in the oxygen uptake in the lungs The increase in the minute output of the heart increases the oxygen supply to the brain A patient with severe pulmonary stenosis and an intact ventricular septum cannot significantly increase the pulmonary blood flow with exercise, and consequently becomes dyspneic on exertion In a patient with pulmonary stenosis and a venous arterial shunt dyspnea may be due to an actual fall in the oxygen saturation of the arterial blood Such a child squats when tired

Polycythemia by which the body tries to compensate for anoxemia, increases the oxygen capacity of the blood and thereby increases the supply of oxygen to *the tissues The capillaries throughout the body become dilated The increase in* the number of red blood cells increases the viscosity of the blood The increased viscosity of the blood may become so great as to cause thromboses and also leads to compensatory changes in the clotting mechanism of the blood

Thromboses may occur anywhere by far the most common site is in the brain (see pages 173–176), but mesenteric and pulmonary thromboses[11] also occur The latter are usually small but widespread throughout the lungs

Brain abscesses are prone to occur when the brain has been previously injured Consequently the repeated minute thrombi in the brain which occur secondary to polycythemia increase susceptibility of the individual to a brain abscess (see pages 176–178)

Purpuric eruptions and dilated hemorrhagic venules especially on the lower extremities, are common in patients with long standing polycythemia These phenomena occur in older patients as the skin loses its normal turgor

Changes in the clotting mechanism of the blood also occur These changes are in a sense compensatory to the polycythemia in that they lessen the danger of thromboses

The blood platelets become reduced in number Not infrequently the platelet count may be only 40,000 to 50 000 platelets per cu mm

The blood fibrinogen is also reduced Hartmann[1] and his associates found that the serum fibrinogen content remained normal but the total blood fibrinogen content was frequently reduced

The clotting time remains normal and the *clot retraction* is also normal The clot, however, may become extremely friable and disintegrates easily[1] *The reduction in the tensile strength of the clot* is undoubtedly an important factor in the hemorrhagic tendency which many of these patients develop It is in all probability a potent factor in the severe postoperative bleeding which frequently occurs in older patients with long standing polycythemia

Although these changes seldom become extreme until early adult life, they occur primarily in patients who have always suffered from oxygen unsaturation of the arterial blood and a severe reduction in pulmonary blood flow These changes are frequently absent in a patient who has had a successful shunt operation even if he fails to maintain the improvement and polycythemia again becomes severe Nevertheless the clotting mechanism should always be studied prior to any operation

Summary

Cyanosis is due to the presence of reduced hemoglobin in the circulating blood in such amounts as to give a bluish discoloration to the skin at least 5 gm of reduced hemoglobin per 100 cc of circulating blood are necessary to produce this color

The occurrence of cyanosis in a patient with a congenital malformation of the heart is indicative of a gross cardiac abnormality In the vast majority of such cases there is some malformation of the great vessels, and a large volume of venous blood is pumped directly into the systemic circulation The intensity of the cyanosis varies with the height of the available hemoglobin and the degree of the oxygen unsaturation of the arterial blood

The oxygen saturation of the arterial blood is altered by factors which act on the systemic circulation and those which act on the pulmonary circulation The

principal factors which operate on the systemic circulation are the volume of the venous blood shunted into the systemic circulation and the amount of reduced hemoglobin in the blood so shunted, the rate of circulation of the blood, the rate of utilization of oxygen in the peripheral tissues, and the rate of removal of venous blood The factors which operate on the pulmonary circulation are the vital capacity of the individual, the rate of the flow of blood through the lungs, and the partial pressure of the oxygen in the inspired air In addition to these *there are three outstanding* causes of cyanosis which are the result of abnormalities in the pulmonary circulation (1) an inadequate volume of venous blood directed to the lungs, (2) difficulty in the return of oxygenated blood to the systemic circulation, and (3) failure of the blood to be oxygenated as it passes through the lungs

The pulmonary vascular changes which commonly develop in patients with malformations of the heart are related to the pressure under which the blood is ejected to the lungs When blood is ejected to the lungs under abnormally high pressure, there is intimal proliferation and narrowing of the small pulmonary arterioles These changes further raise the pressure in the pulmonary arteries and increase the venous arterial shunt, but seldom, if ever, alter the permeability of the capillaries Hence, the blood which is returned from the lungs is fully oxygenated

In arteriovenous aneurysms and in extensive cystic disease of the lungs there is failure to oxygenate the blood in its passage through the lungs

X ray examination offers information as to the size of the pulmonary artery and hence of the volume of blood which is directed to the lungs When the pulmonary conus is concave, the pulmonary artery is small, absent, or misplaced If it is small or absent, the lung fields are abnormally clear If there are large blotchy hilar markings, the pulmonary artery is misplaced It must arise posteriorly, hence there is a complete transposition of the great vessels Fullness of the pulmonary conus and a hilar dance in a patient with persistent cyanosis are usually indicative of pulmonary hypertension

Cardiac catheterization is the best method for the study of the physiology of the malformations of the heart It permits the determination of the location, volume, and direction of the shunt, and of the pressure in the various chambers and vessels into which the catheter is passed

The red blood cell count, the level of the available hemoglobin, and the hematocrit also give an indication of whether the arterial blood is fully saturated

The determination of the oxygen saturation of the arterial blood demonstrates the presence of oxygen unsaturation which is insufficient to cause visible

cyanosis The effect of exercise upon the oxygen saturation of the arterial blood may offer evidence as to the existence and the severity of the shunt The effect of the inhalation of oxygen upon the oxygen saturation of the arterial blood shows the existence of some pulmonary factor, but does not indicate its nature

The circulation time may also give evidence of a venous arterial shunt With a large venous arterial shunt, the systemic circulation time is markedly shortened

The bluish discoloration of the skin is best seen in the fingers and toes and in the buccal mucous membranes With persistent cyanosis, there is compensatory polycythemia, and the patient develops clubbing of the extremities Clubbing and cyanosis occurring together in infancy and childhood are indicative of a severe malformation of the heart Cyanosis always precedes clubbing Cyanosis without clubbing indicates that the cyanosis has been slight or is of recent origin The distribution of the cyanosis may offer a clue to the course of the circulation A difference in the intensity of the cyanosis in the upper and lower extremities occurs when the ductus arteriosus is patent and blood is flowing from the pulmonary artery to the aorta If the feet are cyanotic and the upper extremities of normal color, the patient has severe pulmonary hypertension and persistent patency of the ductus arteriosus The distribution of the cyanosis is reversed in patients with a complete transposition of the great vessels and a patent ductus arteriosus

In the neonatal period the physiological fall in the hemoglobin tends to lessen cyanosis Atelectasis tends to increase it Conversely the complete expansion of the lungs lessens cyanosis Occasionally there is cyanosis at birth but with the establishment of the extra uterine circulation there is a reversal in the direction of the shunt which causes cyanosis to disappear This however, is rare Although cyanosis may decrease during the first few weeks of life, it usually reappears and becomes more intense as the ductus arteriosus undergoes obliteration and thereby lessens the volume of mixed venous blood which reaches the lungs for oxygenation

Persistent anoxemia causes stunting of extra uterine growth Therefore, the rate of growth of the infant may give a clue as to the duration and severity of the anoxemia

Complications secondary to cyanosis are mainly due to anoxemia and polycythemia

Anoxemia is frequently far more severe in early infancy than is indicated by the intensity of the cyanosis Some infants die of anoxemia before the development of polycythemia and hence without intense cyanosis

Fever may occur from severe anoxemia

Attacks of paroxysmal dyspnea occur in an infant with a venous arterial shunt

when there is an abrupt fall in the oxygen saturation of the arterial blood For a discussion of treatment, see page 171

Dyspnea is due to anoxia, either because of further lowering of the oxygen content of the arterial blood or because of inability to increase the rate of blood flow to the lungs and hence to increase the oxygen supply to the brain

Polycythemia occurs in an effort to compensate for anoxemia The increased number of red blood cells and the increased viscosity of the blood in turn cause thromboses Thromboses may occur anywhere the most common place is the brain When such thromboses are large they cause a hemiplegia, when small they injure the brain and increase its susceptibility to abscesses For a discussion of treatment, see pages 173–178

Changes in the clotting mechanism of the blood occur in patients with long standing polycythemia There is a decrease in the number of platelets a lowering of the fibrinogen content of the blood, and an increase in the fragility of the blood clot These changes lessen the chance of thromboses but increase the risk of severe hemorrhage The latter possibility must be taken into account at the time of any operation or injury

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CHAPTER V

MEDICAL CARE

THE sound management of patients with congenital malformations of the heart is extremely important As an ever increasing number of malformations can be helped by surgery it becomes of real importance not only to enable these children to survive until the optimum age for surgery but also to have them grow to be well adjusted, useful citizens Experience has shown that the better adjusted a child is prior to operation, the more easily and the better he adjusts to society after operation Fear of death should never be permitted to enter his mind Self pity should not be allowed The child should be treated with the confident expectation that he will live to grow up and become a self supporting citizen

By and large the prognosis is far better than most people can conceive Immediately after birth the heart may enlarge rapidly to adjust to the work required of it by the abnormal extra uterine circulation Although a complete transposition of the great vessels and an obstructive valvular lesion, especially valvular pulmonary stenosis usually lead to progressive cardiac enlargement, most intracardiac shunts place a constant load upon the heart Once the heart has adjusted to the load further increase in the size of the heart is proportional to growth Therefore although the heart may be greatly enlarged at two years of age, it does not follow that the child will die of cardiac failure within the next few years On the contrary, in most instances the heart has become adjusted to its load before two years of age, thereafter there is no further cardiac enlargement Moreover as in normal individuals the cardiothoracic ratio usually decreases as the child grows Such is the favorable sequence of events If, however, there is evidence of progressive cardiac enlargement the nature of the malformation should be studied to ascertain whether operation could be of benefit, if so, it is probably indicated

Although bacterial endocarditis, acute and subacute, does occur in patients with cardiac abnormalities, the risk of death from this cause is not as great as from an automobile accident Consequently this danger should not be allowed to cast a gloom over the person s life Sudden death is extremely rare

GENERAL MANAGEMENT

A cheerful serene attitude helps the child to adjust to his limitations A congenital malformation is a condition with which a person is born and unless corrected by surgery, it is a condition with which he must live throughout his life The more normal his life can be, the better

If the child s color is normal and he is not markedly stunted in growth, friends and neighbors are unaware of the condition, and therefore he can readily be surrounded by a normal atmosphere On the other hand, the cyanotic child who must rest frequently, needs to be handled with particular tact and cheerful confidence It is of the utmost importance not to spoil the child Spoiling inevitably increases his difficulty in adjustment to society and to other children Furthermore, even after successful surgery he will desire special attention The mother should be urged to love her child as she would a normal child and not to spoil him *more* than a normal child

The physician, on his part should be both patient and tolerant with the mother and the child if the child is badly spoiled Many a physician and nurse have been afraid to give medication to a cyanotic baby for fear of precipitating a spell If the doctor is afraid of the spell he should realize how much more the mother fears one No mother wishes to be the cause of the death of her child As a matter of fact, the physician is able not only to treat but also to prevent a spell by the administration of morphine If the child is subject to frequent severe spells, it is wise to give morphine prior to a treatment and sometimes even prior to an examination Fortunately most infants who suffer from such a severe degree of anoxemia can and should be helped by operation Whenever operation is planned the mother and child deserve every consideration before operation After the condition has been corrected or alleviated is the time to cope with behavior problems Indeed many of these difficulties will automatically disappear, thereafter the main problem is not to let them recur

The amount of exercise which these children should and can take varies with the nature of the malformation For young children a rest period before, as well as after the midday meal is often helpful If the heart is of normal size and there is no cyanosis there is usually no need for limitation of activity If the heart is enlarged it is wise to eliminate competitive games and all activities which place a strain upon the normal child The two outstanding malformations which may lead to progressive cardiac enlargement are pulmonary stenosis with an intact ventricular septum and aortic stenosis Furthermore in both conditions cardiac

enlargement precedes symptoms, therefore, a patient with either of these malformations should be observed at yearly intervals for evidence of cardiac strain and not relied upon to limit his own activity. Exercise sufficient to develop one's strength is important, but it should not be carried to the point of exhaustion.

The exercise tolerance of patients who suffer from persistent cyanosis and reduced pulmonary blood flow varies considerably, not only from patient to patient but also for the same patient from day to day. The extremes of heat and cold almost always cause difficulty for cyanotic children. Damp days markedly reduce their exercise tolerance. This is such a constant finding that it seems as if the atmospheric pressure or humidity must affect the volume of the pulmonary blood flow. Dry air is a great boon to these children. Indeed, the dry air of a high altitude may be better tolerated than the damp air of the seashore. Almost every child will say "on good days" he can do thus and so, but "on bad days" he is much more limited. These children limit their own activity, there is no need for the doctor to do so.

An infant with an abnormal heart should never be forced to learn to walk at an early age, but should be permitted to follow his own inclinations. It is quite as serious not to permit a cyanotic child to walk as it is to force him to learn to walk at the earliest possible moment. Although such a child becomes more cyanotic upon exertion, it is essential for him to develop muscular strength. If not exercised, muscles become flabby. This places an additional handicap upon the child. If the muscular development is poor, graded exercises are often of great benefit. This is quite as true after surgery as prior to it.

Squatting is a common habit among children with a tetralogy of Fallot. It is, however, not limited to this group. Patients with other types of pulmonary stenosis which cause a reduction in the pulmonary blood flow and an increase in the systemic blood flow find relief in the squatting position. The reason for this is not clear. It may be that the cutting off of the circulation to the lower extremities increases the pressure in the systemic circulation and thus increases the left-to-right shunt and hence the flow of blood to the lungs. Be that as it may, for this group of children it is an almost instinctive reaction. As the children become older they tend to outgrow the habit, partly because it is no longer necessary and partly because it is unsightly. Successful operation eliminates the necessity to squat.

Constant squatting may cause fallen arches and weakness of the ankles. Such children may need orthopedic care.

Good posture is highly desirable. The occurrence of spinal deformities in pa

tients with malformations of the heart is not rare, for example, a hemivertebra is relatively common in patients with malformations which involve the great vessels In such instances it is quite possible that it was the skeletal abnormality which caused the malformation of the heart by an alteration in the stress and strain on the embryonic vascular bed (see Chapter 1) Regardless of etiology, a real effort should be made to prevent serious deformity in a patient with a hemi vertebra

Special attention should also be paid to the posture of any patient who has had chest surgery Even though a rib is not resected and the bones become nor mally united, chest deformity is very common after cardiac operations Breath ing exercises and a conscious effort to make the child stand erect help to prevent curvature of the spine

EDUCATION

Education is important Whenever possible parents usually desire to have cardiac surgery performed before the child enters school When this is not pos sible or advisable the normal atmosphere of a regular school is always desirable Most of these children can be readily adjusted to a regular school Therefore, only under exceptional circumstances should the child be placed in a special cardiac class If the child is cyanotic, it should be explained to the teacher that the condi tion is not dangerous that consideration is necessary but that there is no cause for undue concern Overprotection or exclusion from school because of the dan ger of infection is a grave mistake Other children in the household usually in troduce the common contagious diseases of childhood Furthermore, children with cardiac defects usually survive such infections remarkably well

IMMUNIZATION

Prophylactic immunization is quite as important for these children as for the normal child the presence of a cardiac abnormality is not a contraindication to immunization

Diphtheria toxoid or combined diphtheria and tetanus toxoid should be given regardless of the nature of the malformation Diphtheria is more not less serious for these children than for the normal child

Pertussis vaccine and *vaccination against poliomyelitis* are also strongly indi cated

Smallpox vaccination is given preferably in early infancy and is usually re quired before the child enters school If the condition of the infant appears pre

carious or the child has had repeated illnesses, vaccination can be postponed In the average American city smallpox is so completely under control that one unvaccinated child is no menace to society Should an epidemic occur, the child can be immediately vaccinated

DENTAL CARE

The teeth should receive good care Although the possibility of subacute bacterial endocarditis following dental extraction is well known, it is a grave mistake to refuse to fill or extract a tooth because the child has a malformed heart Indeed a decayed tooth is a potential source of infection which may cause subacute bacterial endocarditis or a brain abscess Therefore, good dental hygiene is essential Filling a cavity is preferable to extraction Should the child develop severe dental caries, there is no malformation of the heart in which extraction is contraindicated or in which the use of a local anesthetic is dangerous

Prior to dental extraction the prophylactic administration of a suitable antimicrobial agent is always indicated For young children it is a wise precaution for those over ten years it is imperative Penicillin is now (in 1960) the drug of choice It should be administered prior to extraction in a sufficiently large dose to give a high concentration of the drug in the blood stream at the time of extraction, and an effective level should be maintained until the wound has healed Finland s[1] recommendation of 600 000 units of aqueous procaine penicillin combined with 200,000 units of sodium penicillin G or potassium penicillin G with or without the addition of 0 5 to 1 0 gm of streptomycin given as a single injection just before dental extraction is highly satisfactory The addition of streptomycin is recommended especially for patients who are on continuous penicillin prophylaxis at the time of the dental extraction

Such prophylactic therapy should be given not only to every patient with a cardiac abnormality but also to every patient who has had cardiac surgery, with the possible single exception of a closure of the ductus arteriosus During a ten year period no case of subacute bacterial endocarditis has been reported in a patient after successful closure of the ductus arteriosus therefore, prophylactic therapy may not be necessary for these patients Nevertheless during this ten year period most of these individuals have received the benefit of prophylaxis Without this precaution the record might not have been so good For this reason it seems to the author wise to continue to give these patients the benefit of prophylactic therapy

TONSILLECTOMY

Repeated throat infections are bad for any child For a person with a cardiac abnormality there is the added danger of subacute bacterial endocarditis Enormous tonsils lessen the breathing space in the nasopharynx and thereby may in themselves cause respiratory difficulty Therefore the indications for tonsillectomy are slightly greater for these children than for a normal child with the single exception of a child with a truncus arteriosus and reduced pulmonary blood flow In a truncus arteriosus the pulmonary circulation depends upon the pressure in the systemic circulation If the pulmonary circulation is meager a sudden drop in systemic pressure such as can occur during operation may be fatal (see Chapter xiv)

Every child with a malformation of the heart should have the benefit of a longer hospital stay than is usually indicated for the normal child It is extremely important for the patient to receive therapeutic doses of some antimicrobial agent immediately prior to and following tonsillectomy The dosage and the principle of the administration of these agents are the same as for dental extraction As in dental extraction, the antimicrobial agent should be continued until the wound has healed

OTHER OPERATIONS

Patients with congenital malformations of the heart usually tolerate operations quite as well as normal individuals Therefore routine operations such as appendectomy need not cause undue concern If the operative field is sterile there is no need for the prophylactic administration of antibiotics or chemotherapy When the operation is to be long and severe and the cardiac reserve is low digitalis may be indicated prior to operation The important exception to this statement concerns cardiac surgery in which the ventricle is opened under such circumstances the use of digitalis is controversial (see Chapter xxiv)

ANESTHESIA

Anesthesia is generally well tolerated provided it is given by an experienced anesthesiologist In general cyanotic children should receive oxygen in high concentration throughout the period of anesthesia The choice of the anesthetic agent should be left to the surgeon and the anesthesiologist They should use whatever they find is most satisfactory both will operate better under familiar conditions

Patients with *severe pulmonary stenosis* and *cyanotic children* with increased circulation to the lungs are slow in their response to the inhalation of any anesthetic agent this calls for care, but should not cause undue concern

Primary pulmonary hypertension is virtually the only abnormality which calls for special anesthesia These patients are prone to be extremely sensitive to barbiturates Deaths have been reported from the use of sodium pentothal Whenever possible it is usually advisable to operate under local anesthesia

An auricular septal defect is virtually the only malformation in which there is no visible cyanosis and in which operation may cause a reversal in the direction of the shunt This danger is, however, quite as likely to occur in association with the psychic disturbance of a local anesthesia as with a general anesthesia Such a shunt reversal is usually of short duration and is not a contraindication to surgery

INTERCURRENT ILLNESS

Children with malformations of the heart survive intercurrent illnesses remarkably well Indeed, a malformation of the heart seldom significantly alters the prognosis All such illnesses should be handled according to the best known therapeutic measures It is only the susceptibility of these patients to acute and subacute bacterial endocarditis and to brain abscess which increases the inherent danger of any illness It is, however, worthy of note that with the single exception of the occurrence of subacute bacterial endocarditis following dental extraction, both bacterial endocarditis and brain abscesses occur more frequently without any known antecedent illness than following an acute infection Nevertheless, the susceptibility of these patients to such infections is real, and the difficulty of cure is great, therefore, the prompt administration of adequate chemotherapy or antimicrobial agents in full dosage is strongly indicated whenever a septicemia is suspected

PNEUMONIA AND PULMONARY INFECTIONS

Patients with great cardiac enlargement, especially those with increased pulmonary blood flow are extremely susceptible to pulmonary infections Such infections should be treated with appropriate measures including antimicrobial agents Indeed, in this group of patients continuous prophylaxis is usually of great benefit in the prevention of infection

It is also important to remember that the differential diagnosis between cardiac failure and a pulmonary infection is not always easy Rales in the lungs

may be due to the pulmonary infection or they may result from decompensation Moreover, the x ray shadows in the two conditions may be closely similar With decompensation the respiratory rate increases out of proportion to the other findings and the dilatation of the alae nasae is less conspicuous than in pneumonia In infants and young children engorgement of the liver is one of the early signs of cardiac failure Therefore, the size of the liver usually offers a clue as to the state of compensation If repeated bacteriological studies fail to reveal any pathogenic organism, the strong presumptive evidence is that the condition is primarily the result of decompensation Often the illness is due to a combination of a pulmonary infection and cardiac failure The pulmonary infection should be treated with its appropriate therapy and the cardiac failure with digitalis and other appropriate therapeutic measures (see pages 182 ff)

ACUTE AND SUBACUTE BACTERIAL ENDOCARDITIS

Patients with cardiac abnormalities with the single exception of those with auricular septal defects, are extremely susceptible to acute and subacute bacterial endocarditis Whenever bacteria enter the blood stream, there is danger that the bacteria which circulate through the heart will be driven by the abnormal currents into the interstices of the myocardium or be caught on the roughened endocardium of the malformed heart, causing endocarditis This is notoriously true of the relatively avirulent alpha streptococcus A transitory septicemia due to this organism is of no serious consequence to the normal individual If, however, the organisms become lodged within the heart the fungating mass is difficult to eradicate, the resultant bacterial endocarditis is proportionally difficult to cure

Although a treatise on subacute bacterial endocarditis is beyond the scope of this book, there are a few factors which have special bearing on congenital malformations of the heart Inasmuch as the myocardium is not diseased the prognosis for recovery is far better than when the infection is superimposed upon a heart previously damaged by rheumatic fever Nevertheless the fungating mass is likely to lodge at a point of constriction and thus increase the obstruction There is also the danger that the infection may injure the valves and thereby place an additional strain on the heart Consequently a patient should be kept under close observation after the infection has been cured in order to ascertain whether there has been any alteration in the work required of the heart

The location of the vegetations varies with the nature of the malformation The bacteria lodge where they are driven by the abnormal currents of blood For example in ventricular septal defect the vegetations usually form in the outflow

tract of the right ventricle, where the blood which is shunted through the septal defect impinges against the wall In a patent ductus arteriosus the first vegetations usually develop at the pulmonary end of the ductus, whereas in subaortic stenosis they are caught on the subaortic shelf or on the valve above it

The cardiac findings may be altered by the development of acute or subacute bacterial endocarditis These changes depend upon the location of the fungating mass For example, with a ventricular septal defect the fungating mass develops beneath the pulmonary valve, thus causing a murmur and thrill maximal over the pulmonary area similar to those of pulmonary stenosis In patients with a tetralogy of Fallot who have had a Blalock Taussig anastomosis, the fungating mass may develop at that site and cause thrombosis of the anastomosis

A positive blood culture is usually obtained more easily from a cyanotic than from a non-cyanotic patient In the former the shunt is usually from right to left consequently, the bacteria are thrown off into the systemic circulation In most instances in which the patient shows no cyanosis, the shunt is left to right, and therefore the first bacteria are thrown off into the lesser circulation Under such circumstances pneumonia and pulmonary infarcts are early signs of acute or subacute bacterial endocarditis petechiae and enlargement of the spleen are late manifestations In cases with a left to-right shunt, in the early stages of the disease it may be extremely difficult to obtain a positive blood culture Even when the bacteria reach the systemic circulation they may be filtered out through the capillaries of the body, thereby rendering the venous blood sterile Under such circumstances an arterial blood culture may be positive when a culture taken from venous blood is sterile In all cases in which subacute bacterial endocarditis is suspected an assiduous effort should be made to establish or exclude the existence of the disease and to determine the nature of the infecting organism because the treatment is long and both the prognosis and the treatment vary with the infecting organism

In the vast majority of cases a positive blood culture, if obtainable at all, is obtained on the first or second blood culture Indeed Griffith and Levinson showed that in a series of over one hundred cultures, 98 per cent of the positive blood cultures were obtained in the first five cultures Therefore, regardless of whether or not a positive blood culture is obtained in the presence of clinical evidence of subacute bacterial endocarditis, treatment should never be withheld for more than one week Indeed, after resection of a coarctation of the aorta if acute bacterial endocarditis is suspected a single blood culture should be taken and treatment immediately instituted as any delay in treatment may be fatal

Penicillin or a bacteriocidal agent is always preferable to a bacteriostatic drug in the treatment of subacute bacterial endocarditis It is often desirable to combine streptomycin with penicillin It should be remembered that there are many antimicrobial agents For a resistant organism various combinations of these agents may be preferred to penicillin alone This is especially true in the treatment of enterococcal infections, in which the combination of streptomycin and penicillin is more effective than either one alone [3] Disease due to a staphylococcal infection is far more serious and more difficult to cure than one due to a streptococcal infection For this reason such an infection also usually calls for the administration of large amounts of one or another specific antimicrobial agent in addition to penicillin

Whenever possible it is desirable to test the sensitivity of the infecting organism to penicillin Nevertheless, many strains which are relatively insensitive to the drug can be ultimately eradicated by prolonged treatment with high doses of penicillin

Most authorities prefer to start with an enormous dose—12 million units daily This amount can be given intravenously for seven to ten days thereafter once the evidence of active infection has been controlled the dose is gradually decreased

The mode of administration can be varied with the condition of the patient The all important factors are the proper choice of the drug or drugs the attainment of an adequate blood level and the length of treatment It is unimportant whether these are attained by intravenous, intramuscular or by oral administration For the patient s comfort whenever it is possible oral administration is preferable

Prolonged treatment with penicillin is always advisable Treatment should be continued for a minimum of six to eight weeks after the patient is afebrile It must, however be remembered that the manifestations of penicillin allergy may simulate those of the infection If it seems possible that such is the cause of the continued fever it may be wise to discontinue the drug for a few days and thereby evaluate the effect of penicillin

After penicillin has been discontinued the patient should be kept under close observation for an additional two weeks to be certain that the infection has been eradicated The recurrence of fever or symptoms will necessitate the resumption of treatment

The *prevention* of subacute bacterial endocarditis is extremely important For this reason as previously mentioned prior to dental extraction tonsillectomy or

any procedure, injury, or situation which might be associated with a bacteremia, the patient should receive adequate therapeutic doses of antimicrobial substances or chemotherapeutic drugs as a prophylactic measure Furthermore, because of the danger of acute bacterial endocarditis, any septicemia should be vigorously treated with appropriate drugs

Prolonged prophylactic chemotherapy or antibiotic therapy such as has proven helpful in the prevention of rheumatic recurrences, has not yet been sufficiently tested to warrant an opinion of its value in the prevention of subacute bacterial endocarditis Considerable study will be necessary to determine the efficacy and the advisability of such therapy Nevertheless, if a patient has had subacute bacterial endocarditis, there is reason to consider the use of prophylactic chemotherapy or antibiotics for life If a patient develops a second attack of subacute bacterial endocarditis while receiving prophylaxis, the physician will at least feel that he has done his best to prevent it

PROBLEMS RELATED TO PERSISTENT CYANOSIS

The most serious complications which occur in patients with persistent cyanosis and polycythemia are due either to anoxemia or to the increased viscosity of the blood

Anoxemia is the outstanding difficulty in early infancy When a large amount of venous blood which is normally destined to go to the lungs for oxygenation is shunted into the systemic circulation the oxygen saturation of the arterial blood is proportionately reduced Polycythemia develops to compensate for anoxemia Consequently the effect of anoxemia manifests itself before polycythemia develops Indeed an infant may die from anoxemia before the development of polycythemia and consequently with minimal or no cyanosis Anoxemia causes stunting of extra uterine growth Furthermore, a sudden drop in the oxygen saturation of the arterial blood may precipitate an attack of paroxysmal dyspnea

Attacks of paroxysmal dyspnea are relatively common in infants and children who suffer from sudden severe anoxemia At the onset of the attack some of these children will cry out and then become deeply cyanotic and gasp for breath Usually there is expiratory difficulty Sometimes an attack is precipitated by feeding by a bowel movement, or by some undue exertion at other times it occurs without any apparent cause These attacks are sometimes so severe that the infant loses consciousness Gradually, as the attack wears off, respiration becomes easier and the infant s color improves

At the onset of an attack of paroxysmal dyspnea the child or infant should immediately be turned on his abdomen and placed in knee-chest position, or held over one's shoulder with his knees doubled up beneath him If the attack is not relieved by such treatment the infant should be given morphine Occasionally artificial respiration and stimulants are necessary Oxygen if given by mask may help but care should be taken to avoid a forceful stream of oxygen A blast of oxygen is as disagreeable to an infant as walking against the wind is to an adult

The action of morphine is almost specific Not only does the child quiet down but his color improves Often one half hour after the intramuscular administration of the drug, a child who has been panting for breath is entirely comfortable and able to run around without difficulty The *dose* is 1 mgm per 4 5 kg of body weight (1 mgm per 10 lb of body weight) In cases of severe paroxysmal dyspnea, three-quarters of the calculated dose may be given intravenously, and if the patient is not promptly relieved, fifteen minutes later the remainder may be given

Frequently, an infant with a tetralogy of Fallot suffers from repeated attacks of paroxysmal dyspnea between the age of six and eighteen months Thereafter, the attacks usually decrease in number and severity, and after two years of age the child begins to show improvement The improvement comes with the development of compensatory polycythemia and with the development of collateral circulation In general, if the infant has a harsh systolic murmur and the attacks of paroxysmal dyspnea are readily relieved by the knee-chest position the prognosis for life is good If, however, the infant has a small heart, clear lung fields and no murmur there is great danger that he will die from anoxemia For such infants an operation which increases the pulmonary blood flow may be life saving (see Chapter VI)

Failure to gain weight at a normal rate may be due to a large left to-right shunt or to severe anoxemia An infant with a large left to-right shunt eats well but gains very slowly An infant who suffers from severe anoxemia has difficulty in the digestion of food For such an infant, small and frequent feedings are often helpful

Cessation of weight gain is of grave prognostic import it is therefore a strong indication for operation Fortunately many of these infants suffer from inadequate circulation to the lungs and can readily be helped by a systemic-pulmonary anastomosis

Constipation is a common complaint, especially in weak cyanotic infants Not

infrequently the effort required for a bowel movement precipitates a spell A real effort should be made to overcome this difficulty Sometimes cod liver oil instead of a concentrated vitamin preparation is all that is necessary Prune juice or a little senna tea may relieve the condition, mineral oil or milk of magnesia in appropriate doses may help If these measures are not effective, a small soap suppository given at the time of the bowel movement is advisable

Fever is relatively common in patients with severe anoxemia Although the persistence of low grade fever may lead to the suspicion of subacute bacterial endocarditis or brain abscess if no other evidence of infection can be elicited, the occurrence of fever in a patient with severe anoxemia is strong indication for an immediate operation to increase the volume of venous blood directed to the lungs

Anemia occurs quite as readily in infants with a venous arterial shunt as in normal infants The level of the hemoglobin may not be as low as in a normal infant but the amount of oxygen available to the tissue depends upon both the amount of available hemoglobin and the oxygen saturation of the arterial blood If the oxygen saturation of the arterial blood is only 50 per cent, which is relatively high for a cyanotic child the amount of available oxygen is but half that indicated by the level of the available hemoglobin Experience has shown that most cyanotic infants thrive if the hemoglobin level can be maintained at 15 gm per 100 cc of circulating blood A constant effort should be made to maintain the hemoglobin at this level Not infrequently in the presence of an infection the infant will develop an anemia and severe attacks of paroxysmal dyspnea Such attacks may markedly diminish in frequency and in intensity and in some instances entirely disappear with the correction of the anemia Therefore if the *anemia is severe a small blood transfusion is often extremely beneficial* If, however the infant is subject to attacks of paroxysmal dyspnea, he should receive a full dose of morphine prior to the transfusion The treatment of anemia with intramuscular iron may be of great benefit to such a patient

The administration of iron is strongly indicated for a cyanotic infant with a hemoglobin of 12 gm or less The level of the hemoglobin should always be closely followed while the baby is receiving iron, because the response may be so rapid that he may develop severe polycythemia, and that in itself will cause difficulty

Headaches are common in patients who suffer from anoxemia or polycythemia and may occur in patients with severe hypertension or an excessively wide pulse pressure These individuals frequently complain of headaches follow

ing exercise Such headaches may be indication for operation, provided operation will relieve the cause of the headaches

Sustained mental effort may be tiring to a person with a low oxygen saturation of the arterial blood or a marked reduction of the systemic blood flow For such a child corrective surgery may be of great benefit

Mental retardation is not caused by anoxemia Therefore an increase in the oxygen supply to the brain will not appreciably alter the child's intelligence Furthermore, a strong body with a weak mind is a liability to society For this reason severe mental retardation is a contraindication for operation

Polycythemia and collateral circulation develop in an effort to compensate for the lowered oxygen saturation of the arterial blood The increase in the number of the red blood cells and in the level of the available hemoglobin raises the oxygen saturation of the arterial blood and thereby improves the supply of oxygen to the tissues Nevertheless, the increased viscosity of the blood may cause complications, the commonest and most serious of such difficulties are thromboses

THROMBOSES

Thromboses may occur anywhere By far the most common sites for serious thromboses are the brain and the lungs

Cerebral thromboses are the most common they occur frequently in infants under two years of age with severe anoxemia and in adults with long standing polycythemia Children are relatively free from this complication

An infant may suddenly lose control of one limb and immediately thereafter show signs of a hemiplegia Such paralysis generally occurs abruptly, and shortly thereafter the patient shows gradual improvement but is usually left with a residual hemiplegia If the thromboses are extensive, the infant may cry out for weeks thereafter and show mental disorientation similar to that of an adult after a severe stroke

Cerebral thromboses occur in infants with severe anoxemia before the development of marked polycythemia Tyler[4] has shown that cerebral thromboses are common under the age of two years when the oxygen content of the arterial blood is below 10 volumes per cent or when the red blood cell count is over 7 5 million per cu mm Dehydration greatly increases the danger of thromboses For this reason thromboses are prone to occur in hot weather or during a febrile illness, hence at such times a high fluid intake is imperative Occasionally cerebral thromboses are ushered in by convulsions which may be long and severe

Upon the first signs of impending thrombosis an immediate effort should be made to dilute the blood and to lengthen the coagulation time The occurrence of a cerebral thrombosis calls for prompt and vigorous therapy because if treatment is established within the first six hours there may be no residual signs of a hemiplegia

Venesection may be of great benefit if performed within six hours after the development of a cerebral thrombosis A child between two and six years of age with severe polycythemia will be benefited by the withdrawal of 100 to 250 cc of blood, depending on the age and the size of the child and the height of the *red blood cell count Venesection should be accompanied by oxygen therapy* and combined with the intravenous administration of saline, 5 per cent glucose, dextrin, or some plasma expanding fluid If plasma is given to a patient with polycythemia the plasma should be cross matched with the patient s cells because the increased number of red blood cells increases the danger of a transfusion reaction Nevertheless, the administration of intravenous fluid is necessary not only to replace the blood withdrawn but also to combat the increased viscosity of the blood and to prevent further hemoconcentration

It is extremely important to maintain an adequate fluid intake until the patient is again able and willing to take fluids by mouth For this reason, a continuous *intravenous infusion is frequently necessary for twelve to twenty four hours* after venesection Part of the fluid may be in the form of normal saline, and the remainder should be 5 per cent glucose Hypertonic glucose should never be given to patients with polycythemia

The value of anticoagulant therapy is controversial In the presence of cerebral hemorrhage it is clearly contraindicated In most young patients the blood vessels are normal, and there is virtually no danger of hemorrhage If anticoagulants are given within a few hours after the development of a hemiplegia *there may be no residual paralysis Heparin acts more promptly than does* dicumarol, and therefore is the drug of choice The initial dose should be given intravenously and should be sufficient to prolong the clotting time of the blood to twenty or thirty minutes The prolongation of the clotting time should be maintained by the continuous administration of the drug over a period of ten to twenty four hours This is most easily accomplished by the addition of heparin to a continuous intravenous drip of normal saline or 5 per cent glucose

The dose of heparin is approximately 0 5 mgm per kg of body weight The initial dose, if given intravenously promptly causes a prolongation of the clotting time It requires approximately the same amount of heparin per hour to

keep the clotting time at a given length as it does to prolong it to that extent For example if the child weighs 20 kg 10 mgm of heparin are given intravenously and 10 mgm of heparin are added to each 100 cc of 5 per cent glucose given intravenously per hour If it is necessary to slow the drip so that but 50 cc of fluid are given per hour, it is usually necessary to increase the amount of heparin in the solution The clotting time must be closely followed, and the amount of heparin increased or decreased to maintain the clotting time at approximately twenty to thirty minutes If the clotting time tends to return to normal more heparin should be given intravenously and additional heparin should be added to the infusion If, however, the clotting time becomes unduly prolonged, more saline or 5 per cent glucose should be added to the flask If the clotting time becomes greatly prolonged, heparin should be discontinued and a solution of 5 per cent glucose without heparin given until the clotting time shortens If the clotting time becomes excessively prolonged it may be brought back to normal by the use of protamine. The dose of protamine required to counteract the action of heparin is the same milligram for milligram as the amount of heparin which has been given A smaller amount of protamine will reduce but not abolish the effect of the heparin If bleeding should occur, a small blood transfusion may be necessary This procedure, by itself, usually brings the clotting time to normal

When the above therapy is promptly instituted the results are extremely gratifying indeed in most instances there is no residual hemiplegia

Blindness is the most tragic of all complications Fortunately it is rare, but the author has seen two patients in whom cerebral thrombosis caused permanent blindness Both patients were French children with extreme polycythemia, who had received a low fluid intake over a long period of time These two cases constitute a strong argument for the maintenance of a high fluid intake for patients with marked polycythemia

Pulmonary thromboses are common These thrombi are usually microscopic in size but may be extremely numerous throughout the lungs Rich[5] first demonstrated the frequent occurrence of such thrombi in patients dying from cyanotic heart disease He pointed out that there was also recanalization and suggested that this phenomenon of thrombosis and recanalization might be responsible for the periods of aggravation and remission of symptoms which these patients so frequently experience Ferencz[6] in her detailed study of pulmonary vascular changes found a remarkably high incidence of recent thrombi in the lungs of infants who had died during spells of anoxia The relation of the one to the other is however not yet clear

Mesenteric thromboses are rare The author has seen two such instances associated with abdominal distension and gross blood in the stools One of these occurred after a day of nausea and vomiting during which the child had become severely dehydrated and then comatose, and consequently had taken virtually no fluid for twenty four hours The other occurred after an operation before the patient was taking fluids well

BRAIN ABSCESSES

Brain abscesses are relatively common in patients with a venous arterial shunt In such persons blood is shunted into the systemic circulation without passing through the lungs, where the bacteria are normally filtered out It is apparently the occurrence of the shunt, not the severity of the anoxemia or the extent of the polycythemia, which renders the patient susceptible to such an infection Nevertheless, the normal brain is remarkably resistant to bacterial infection Indeed, in the experimental animal massive doses of bacteria may be injected directly into the cerebral artery without the formation of an abscess A minute injury to the brain, however renders the animal susceptible to abscess formation Thus two factors appear necessary a venous arterial shunt and brain injury Nevertheless, it is a striking fact that although patients with long standing polycythemia may have multiple minute thrombi in the brain, multiple abscesses are not common Indeed, if there are multiple abscesses they are seldom scattered throughout the brain such abscesses, when they do occur, are usually daughter abscesses or extensions from the original focus of infection This finding is in striking contrast to the multiple brain abscesses which develop in persons with chronic pulmonary infections and normal circulation The explanation for this is not clear Furthermore, brain abscesses are rare under two years of age

The onset is insidious Clinical manifestations appear only as the abscess increases in size

Headache sharply localized to one specific point, is a common complaint This type of headache must be differentiated from the diffuse generalized headache which so commonly occurs after exercise in a patient with severe polycythemia The pain may be so sharply localized that the patient can point to the area which is directly over the abscess Thus, in many instances, the patient can show the neurosurgeon where the burr hole should be made

Percussion tenderness may be demonstrable over the abscess

Persistent low grade fever or *recurrent episodes of high fever* for which no adequate explanation can be found should arouse suspicion Indeed, in any pa

tient with a venous arterial shunt in whom subacute bacterial endocarditis is suspected but cannot be proven the possibility of a brain abscess should be entertained

Lumbar puncture frequently reveals some abnormality, either an increase in the number of cells, an increase in the protein, or an increase in pressure The last mentioned is, however, rarely seen in the early stages of a brain abscess

Careful neurological examination is always indicated and frequently reveals some localizing signs Evidence of progression or extension of any such sign is highly suspicious of a brain abscess

Convulsions are relatively common and may be the initial symptom Indeed in a patient over two years of age when a convulsion ushers in a hemiplegia the hemiplegia is more frequently due to a brain abscess than to a cerebral thrombosis

The differentiation of a brain abscess from a cerebral thrombosis is important Cerebral thromboses are common under the age of two years whereas brain abscesses are rare in this age group A cerebral thrombosis usually occurs abruptly The patient suddenly develops a hemiplegia and thereafter gradually improves Frequently in the presence of a brain abscess, the signs of a hemiplegia develop gradually and until the abscess is drained there is usually a progression of signs and symptoms

Personality changes are more common with brain abscesses than with cerebral thromboses

Nausea and vomiting choked discs and *signs of increased intracranial pressure* are rare with a cerebral thrombosis and relatively common with a brain abscess

Bradycardia especially the sudden slowing of the pulse rate is a late and ominous sign Its occurrence calls for the immediate drainage of the abscess Terminally, the abscess frequently ruptures into the meninges, and the patient dies from a fulminating meningitis

The diagnosis of a brain abscess is not easy, especially when the patient is seen early Neurological consultation is often helpful An electroencephalogram may be of aid in the localization of an abnormality or in the demonstration of an expanding lesion. Severe headache, fever, and signs of neurological difficulty, especially if there is a history of convulsions are far more probably due to a brain abscess than to a cerebral thrombosis Indeed, a brain abscess should be suspected in a cyanotic patient with unexplained fever especially if it is recurrent Occasionally a lumbar puncture gives the clue

A brain abscess seldom, if ever, cures itself, it almost invariably requires surgical drainage Therefore, whenever there is a high degree of suspicion, a neurosurgeon should be called in consultation This is especially important as an abrupt change in the patient s condition may occur which necessitates an emergency operation It is inconsiderate to have a patient under observation for several weeks and not consult a neurosurgeon until an emergency operation becomes necessary Moreover, the chances of cure are directly proportional to the promptness with which the diagnosis is made With early diagnosis and proper treatment the chance of recovery is extremely good Without treatment the condition is almost invariably fatal

Whenever time permits, massive doses of antimicrobial agents are strongly indicated prior to the drainage of the abscess and should be continued until all evidence of infection has subsided

The extent of improvement which is possible after a severe brain abscess is extraordinary The author has seen one child who was unconscious and unresponsive for two months who eventually made an almost complete recovery

The danger of focal epilepsy after a brain abscess is however, so great that anticonvulsant drugs are usually indicated for life Although the author does not believe that all brain abscesses could be prevented by the prophylactic administration of antimicrobial or chemotherapeutic agents, it seems probable that such therapy would reduce the incidence A second brain abscess would inevitably further injure the brain Therefore, it is a wise precaution to give these patients some prophylactic antimicrobial agent for life

A successful anastomosis does not eliminate the danger of brain abscess It remains to be seen whether total correction eliminates this complication or whether the injury to the brain from the previous polycythemia leaves the individual unduly susceptible to such infections

TUBERCULOSIS

Although it is frequently believed that cyanotic persons are unusually susceptible to tuberculosis, in the author s experience the incidence of tuberculosis in cyanotic patients in the United States has not been unduly high Nevertheless, in Sweden and Norway following World War II, a high incidence of tuberculosis was found among the children who had a tetralogy of Fallot Thus it seems that cyanotic patients are prone to tuberculosis only if placed in unfavorable circumstances In other words, their resistance is not as high as that of the average person with a normal circulation

The experiments of Hanlon, Scott Olson, and Mattern[7] are in accord with the clinical observation that the reduction in the oxygen saturation of the arterial blood does not render the person unduly susceptible to tuberculosis These investigators[8] found the reverse to be true in monkeys infected with tubercle bacilli They tested the effect of experimental inoculation both before and after the creation of a systemic pulmonary arterial anastomosis The tuberculosis was uniformly more severe in the area where the oxygen content of the blood was higher than normal Further, after an end to-end anastomosis was performed, the infection was much more severe on the side of operation than on the unoperated side Therefore, it has been our considered policy that a patient with tuberculosis should have an end to-end anastomosis on the opposite side to the tuberculosis lesion Twice has such an operation been performed on patients with arrested tuberculosis with no untoward effects

OTHER COMPLICATIONS

Hemoptyses although rare in patients with reduced pulmonary blood flow are common in older cyanotic individuals with excessive pulmonary blood flow and pulmonary hypertension The hemoptysis is usually due to the rupture of or oozing from a small pulmonary vessel in which the pressure is excessively high It may also be related to changes in the clotting mechanism of the blood as hemoptyses seldom occur in a patient with a normal oxygen saturation of the arterial blood but do occasionally occur as a late complication in a patient with a severe pulmonary stenosis and tremendous development of the collateral circulation A patient who is prone to hemoptysis may be helped by an occasional phlebotomy (see below)

Excessive bleeding following injury or operation may occur in patients with long standing polycythemia The difficulty is undoubtedly related to the changes which occur in the clotting mechanism of the blood (see page 155) Phlebotomies, which temporarily increase the number of the blood platelets may lessen the danger of hemorrhage For this reason, the clotting mechanism of the blood should always be studied prior to operation on a patient with severe polycythemia

Muscle cramps and *pains in the limbs* are of common occurrence in older cyanotic individuals These pains are probably in part due to an inadequate supply of oxygen to the tissues Such pains may be due to *gout*[9] which occasionally occurs in patients with polycythemia In such instances the uric acid level of the blood is elevated The author has known one instance in which the blood uric

acid reached 5 mgm per cent Appropriate therapy will lessen the patient s discomfort

Congenital angiomatous hydrarthroses of the joints, such as are shown in Figure v–1, occasionally occur in patients with congenital malformations of the heart Such individuals may develop tremendous swelling of the joints when polycythemia becomes extreme Swelling of this origin may be markedly reduced with the reduction of polycythemia following successful surgery

TREATMENT

Supportive therapy is especially important because the rapid advances in cardiac surgery mean that many conditions which cannot be helped today, may be able to be helped in the near future

High fluid intake is essential for a patient with polycythemia because it lessens the danger of thromboses A child of one year of age with a red blood cell count of 7 million or over should receive 1000 cc of fluid per day A child between two and five years of age should receive at least 1500 cc daily, and older children a minimum of 2000 cc daily Many adults require 3000 to 4000 cc of fluid per day No cyanotic patient should ever be more than twelve hours without fluid Great care must be taken not to dehydrate a patient prior to operation It is a wise precaution to continue water by mouth until five hours prior to operation This is especially important if the operation is not performed early in the morning or if any special test, such as angiocardiography or cardiac catheterization, is to be performed later in the day If breakfast is to be withheld the patient should receive additional fluid during the night

Phlebotomy offers temporary relief to a patient with severe polycythemia It is however, only a palliative measure If nothing is done to relieve the underlying condition, polycythemia will inevitably recur Repeated venesections are extremely debilitating Therefore, repeated phlebotomies should be used as a last resort only when the condition is inoperable, as, for example, when a patient with increased pulmonary blood flow and pulmonary hypertension is subject to hemoptyses Some of these patients can tell when such complications are impending and at such times the patient may be benefited by a venesection

Patients with cerebral thrombosis may also be benefited by a venesection (see page 174)

In patients with long standing polycythemia venesection is frequently indicated prior to surgery in an effort to increase the blood platelets and to improve the clotting mechanism of the blood One or more phlebotomies of 500 cc of

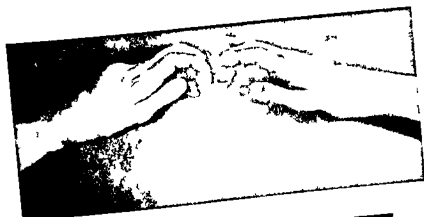




FIGURE 5–1 Congenital angiomatous hydrarthrosis

blood may be necessary A venesection, however, should never be performed to improve the clotting mechanism of the blood without a knowledge of the oxygen saturation of the arterial blood In a patient with an arterial oxygen saturation of 50 per cent venesection may be done with proper caution If the arterial oxygen saturation is under 30 per cent, venesection is contraindicated All phlebotomies must be done with great caution, as such a patient frequently has a severe reaction during the procedure The patient should receive oxygen continuously throughout the procedure and probably for the ensuing twelve to twenty four hours The volume of blood withdrawn should be immediately replaced by normal saline, 5 per cent glucose, or some plasma expanding fluid This is important in order to prevent hemoconcentration with its inherent danger of thrombosis Plasma, if given at all, must be given with the greatest of care, as it frequently causes a severe, even fatal, anaphylactic reaction in a patient with extreme polycythemia

By and large phlebotomies are contraindicated and should seldom be done solely because of a high hematocrit

CARDIAC FAILURE

Cardiac failure should not be considered as an inevitable terminal event for a patient with a congenital malformation of the heart Even after the development of decompensation, if appropriate therapy is instituted, a number of these patients may still enjoy many years of life The proper treatment of cardiac failure is especially important as a large and steadily increasing number of malformations can be corrected by surgery

Cardiac failure may be caused by the burden placed on the heart by the structural abnormality, by the strain of an intercurrent illness, or by some superimposed infection of the myocardium Occasionally it is precipitated by the development of an arrhythmia, notably paroxysmal tachycardia, auricular flutter, or auricular fibrillation In infants cardiac failure, especially when associated with great cardiac enlargement and a malformed heart, is almost invariably due to the structural abnormality of the heart In older children and young adults, the rupture of an aneurysm from the sinus of Valsalva into the lesser circulation (see Chapter xxv) is an additional cause of the abrupt onset of cardiac failure In older individuals a low cardiac reserve and diminished coronary flow may be responsible for gradual cardiac failure

The signs of cardiac failure vary with the age of the individual In an infant the first signs of cardiac failure are engorgement of the liver and increase in the

respiratory rate Although the liver enlarges rapidly, it is usually soft but it is seldom tender For this reason gentle palpation is required to determine its size In addition, the infant s respirations become extremely rapid, 60 to 70 per minute or more He often breathes quietly therefore, unless the respirations are counted the extreme rapidity of the respiratory rate may be overlooked Even when there is adequate circulation to the lungs, rales at the bases of the lungs are a late manifestation of cardiac failure, and so is edema of the extremities

In a child the respiratory rate is the most sensitive index of cardiac compensation When the respirations reach 30 per minute, the liver begins to enlarge With respirations of 40 per minute, the lower margin of the liver is almost always at the level of the umbilicus Therefore unless there is engorgement of the liver and the respiratory rate is rapid, rales at the lung bases should not be considered an indication of decompensation The differentiation of pulmonary infection from decompensation is extremely important as pulmonary infections are common in patients with great cardiac enlargement and require different therapy

In an adult rales at the lung bases and edema of the extremities are early signs of cardiac distress

The treatment of cardiac failure and the drugs available are the same for all ages Patients with cardiac failure should be treated with rest, venesection, oxygen diuretics, and digitalis A safe and simple rule for all medication is to adjust the dosage in direct proportion to the body weight The average adult dose is based upon a body weight of 150 lb A child who weighs 50 lb should receive one third of the adult dose For a 15 lb baby the dose is one tenth of the adult dose

Rest is a great therapeutic measure It is imperative for all critically ill patients If not obtained readily sedation should be freely used Rest in itself is beneficial the relief from mental anxiety is also important

The barbiturates relieve mental anxiety Morphine and codeine relieve pain Repeated doses of morphine are liable to cause abdominal distention Therefore for prolonged use codeine or other derivatives of opium are to be preferred Paraldehyde in oil given by rectum, is a safe drug A child of six to eight years will often be quieted for ten to twelve hours by 4 to 6 cc of paraldehyde given by rectum It is however seldom needed in infancy

Oxygen is of great help both to patients with cardiac failure and to those who suffer from anoxemia due to a malformation of the heart In persons who suffer from a large venous arterial shunt, the inhalation of oxygen is helpful only inso-

far as pulmonary factors are contributing to the anoxemia Nevertheless, even if the principal difficulty is inadequate circulation to the lungs or a large venous arterial shunt, pulmonary factors almost always play some role Therefore oxygen is usually beneficial

Venesection is indicated for a patient with acute pulmonary edema If severe pulmonary edema develops during a cardiac operation due to the excessive administration of intravenous fluid, venesection may be life saving It should be done immediately, even though the patient may subsequently require a transfusion

Diuretics are helpful The primary indication for the use of diuretics in an infant is to rid the patient of edema If cardiac failure occurs early, it is indicative of a very serious malformation Therefore, if the infant can be helped by operation, *early operation is usually advisable For this reason long continued use of* diuretics is seldom indicated

The dose of mercurial diuretic is calculated in direct proportion to the body weight it should be based on the estimated edema free weight of the infant For example, if the dose of the mercurial diuretic is 1 to 2 cc for an adult of 70 kg (150 lb) an infant of 7 kg should receive one tenth of that amount, that is, not more than 0 2 cc of the drug, an infant of 5 kg should only receive 0 1 cc

Sodium restriction in infants should be used with caution The infant on a formula receives precisely what is prescribed or less than that if he refuses part of his formula There is no chance for him to cheat and thereby get extra salt Moreover his electrolyte balance is delicate and is easily upset Furthermore, if the infant has been on a low salt diet, the administration of a mercurial diuretic may cause severe renal damage

DIGITALIS AND ALLIED PREPARATIONS

Although the indiscriminate use of digitalis is to be deprecated, the wise use of the drug is often life saving

The indications for the use of digitalis are essentially the same for children as for adults (1) cardiac failure (2) dilatation of the heart and a gallop rhythm, (3) excessively rapid heart action (180 to 200 beats per minute), (4) the occurrence of a serious cardiac arrhythmia such as auricular fibrillation, auricular flutter, and paroxysmal tachycardia (see Chapter xxxi), and (5) occasionally a sudden shunt reversal In infants and children with serious arrhythmias, quinidine (see below) may be of help It is, however, almost always essential to give digitalis first because these arrhythmias unless promptly controlled may lead to severe cardiac failure and even to death

The choice of the preparation depends mainly upon the rapidity with which an effect is desired. Any carefully tested stable preparation of digitalis or its derivatives may be used.

Lanatoside C U.S.P., is extremely useful when a rapid effect is desired. It has the great advantage that it can be given to a patient who is receiving digitalis without taking into consideration the amount of digitalis he has received. It must, however, be used with caution, as the first warning sign of toxicity, namely nausea, is absent, and vomiting occurs late. The total dose is 0.02 to 0.03 mgm. per kg. of body weight. In case of emergency two-thirds of the total calculated dose may be given intravenously as the initial dose and the remainder given two to four hours later. The effect lasts for twenty four to thirty six hours. The theoretical maintenance dose is one half to one third of the total digitalizing dose. It is, however, usually wise to shift to a long acting preparation the following day or, at latest, in a couple of days.

Digoxin is also an excellent preparation when a rapid action is desired. When given intravenously an effect is attained within ten to thirty minutes, and it reaches its full extent in one to two hours. For infants and children the total digitalizing dose is between 0.050 and 0.075 mgm. per kg. of body weight.* To attain a prompt effect one half of the total digitalizing dose may be given intravenously as the initial dose and followed by one-quarter of the total dose in four to six hours and the remainder may be given after a subsequent six hours.

Digoxin has the advantage of rapid action and rapid excretion. The entire amount is normally excreted by the kidneys in three days. Therefore, in a patient with normal kidney function, the maintenance dose is approximately one third the digitalizing dose. In order to maintain a reasonably constant level of digoxin the maintenance dose is frequently divided into two doses given morning and night. If the drug is given over a period of days or weeks, the dose should be regulated so that neither the child nor the mother is aroused at night.

When a digitalizing effect is required over a long period of time, a slow acting preparation may be preferred as it permits greater flexibility in the time of administration of the maintenance dose. Indeed, failure to give digitalis for a

*The dose for digoxin is frequently given in *micrograms*. A *microgram* is 1/1000 of a *milligram*. Therefore 10 micrograms (mcg.) equal 0.01 mgm. or 50 micrograms equal 0.05 mgm.

1.0 gm. = 1000 milligrams	1.0 milligram = 1000 micrograms
0.1 gm. = 100 mgm.	0.1 mgm. = 100 mcg.
0.01 gm. = 10 mgm.	0.01 mgm. = 10 mcg.
0.001 gm. = 1 mgm.	0.001 mgm. = 1 mcg.

day or even two days does no great harm, but the excretion of one third to two thirds of digoxin may seriously upset the infant s compensation

According to Lown and Levine[10] the total digitalizing dose for adults is be tween 2 0 mgm and 5 0 mgm, with an average of 3 75 mgm For rapid oral digitalization Levine recommends 1 0 mgm as an initial dose, followed by 0 5 mgm every four to six hours until the patient shows evidence of a therapeutic effect The average maintenance dose for adults is approximately 0 5 mgm daily

Digitalis or *digitoxin* are standard useful preparations for the treatment of chronic cardiac failure Although it takes a longer time to attain the full benefit from these drugs, both are extremely satisfactory

The dose of all digitalis preparations is calculated directly proportional to body weight A child usually requires a slightly larger dose in proportion to his body weight than does an adult For complete digitalization infants and chil dren require between 33 and 45 mgm per kg of body weight of digitalis and between 0 020 and 0 033 mgm per kg of body weight of digitoxin If digitaliza tion is to be complete within twenty four hours, the dose for digitalis should be calculated on the basis of 33 mgm per kg of body weight and that for digitoxin on 0 020 mgm per kg of body weight

If an effect is desired within twenty four hours, one half the calculated total dose may be given as the initial dose this should be followed eight hours later by one half that amount, and this dose may be repeated again in eight hours For example, if the baby weighs 3 5 kg the total dose of digitalis calculated on 33 mgm per kg will be approximately 0 115 gm The initial dose would be 0 05 gm (50 mgm) the second dose eight hours later 25 mgm, and eight hours later an additional 25 mgm may be given, thus giving the baby a total of 100 mgm in twenty four hours The following day, unless there is evidence of full digitalization, the infant should receive another dose of 25 mgm When a more rapid effect is desired digoxin is preferable

If slow digitalization is desired, a total dose of digitalis, calculated on the basis of 45 mgm per kg of body weight may be given over a period of three days Under such circumstances the estimated total amount is divided into six equal doses which are given at twelve hour intervals

The methods for administration of digitalis are similar for all ages If the patient is acutely ill, in order to insure the absorption of the drug the drug should be given intramuscularly or intravenously Unless there is marked edema, intramuscular injection is entirely satisfactory, in infants it is both safer and

easier than the intravenous use of the drug As soon as the patient s condition im proves, digitalis should be given by mouth

Digitalis when given orally to an infant is best given in liquid form Any good preparation of standard potency measured with a graduated medicine dropper will give satisfactory results The drug should be diluted in water and given by teaspoon Digitalis should never be put into the baby s formula because if he refuses any of his formula he receives an uncertain amount of the drug

The first signs of improvement in compensation are the disappearance of a gallop rhythm a decrease in the size of the liver, and the slowing of the respiratory rate The full therapeutic effects are attained before there is any evidence of toxicity Moreover, minor toxic effects are difficult to appreciate in young persons No infant complains of nausea he simply vomits For this reason, infants must be observed with care In case of auricular fibrillation the dose can be regulated by the control of the heart rate This is usually true also in auricular flutter In case of paroxysmal tachycardia, unless the paroxysm comes to an end, digitalis may be given until there are signs of toxicity or marked electrocardiographic evidence of digitalization

The electrocardiogram is often of aid in the regulation of digitalis In order to evaluate the electrocardiographic changes properly, it is important to have an electrocardiogram prior to the administration of the drug Not infrequently a patient with a congenital malformation of the heart, especially one with cyanosis will show depression or inversion of the T waves in Lead I and Lead II Therefore, unless a record has been taken prior to the administration of the drug it may be impossible to determine whether or not the changes are due to digitalis

The maintenance dose of digitalis and of digitoxin is approximately 10 per cent of the total digitalizing dose Thus the daily maintenance dose for an adult is usually 0 1 to 0 2 gm of digitalis or 0 1 to 0.2 mgm of digitoxin Children five to ten years of age require one half this dose Infants require about 10 per cent of the total digitalizing dose for a maintenance dose If there is doubt that the patient is fully digitalized, the maintenance dose may be increased, but the total amount should be divided in halves and given twice daily, on this regime, should toxicity develop it will not be excessive When digitalis or digitoxin is given over a long period of time it is usually wise to omit the drug one day each week in order to prevent slow accumulation of the drug

The withdrawal of digitalis is indicated upon the occurrence of signs of toxicity Digitalis should be withheld until all signs of toxicity have disappeared and

then a maintenance dose should be given Digitalis is usually needed for a period of years Nevertheless, even if an infant requires digitalis for months or years, this does not necessarily mean that he will require it for life There is no need to hesitate to maintain an infant on digitalis until childhood As the child grows his margin of safety increases and there is less danger of serious decompensation upon the withdrawal of the drug Often it will be found that by five or six years of age the heart has adjusted to its load and digitalis is no longer necessary

Broadly speaking if the cardiothoracic ratio is 55 per cent or under, a child with a congenital malformation of the heart does not need digitalis With a cardiothoracic ratio of 55 to 64 per cent he may or may not need the drug, with a cardiothoracic ratio of 65 per cent or over, compensation can seldom be maintained without the aid of digitalis

Cardiac failure is always serious, especially when due to an underlying structural abnormality The larger the heart or the more intense the cyanosis, the more guarded is the prognosis Nevertheless, the author has seen a number of patients with congenital malformations of the heart and severe failure, for whom the outlook was seemingly hopeless, show remarkable recoveries following the use of digitalis Therefore digitalis should always be tried This is especially important if the patient shows no cyanosis Nevertheless, regardless of age, if a patient suffers from cardiac failure due to a structural abnormality of the heart, as soon as the patient s condition permits careful study is indicated in the hope that the condition may be corrected or alleviated by surgery This is especially important in infants, because rapid cardiac enlargement and cardiac failure in early infancy are indicative of a rapidly increasing load on the circulation which may soon be incompatible with life Therefore if help is to come, it must come promptly or it will be too late

Indeed, the occurrence of progressive cardiac enlargement, especially in infancy is an indication for careful evaluation, because if the condition can be corrected by surgery whenever possible it is always preferable to operate before the development of cardiac failure

PAROXYSMAL TACHYCARDIA

Paroxysmal tachycardia is prone to occur when one or both auricles are enormously enlarged and may occur spontaneously in an individual with a normal heart

In an infant the occurrence of paroxysmal tachycardia is far more serious than in an adult as a prolonged tachycardia of 200 per minute or more fre

EXPLANATION OF PLATES

PLATE 1

Fig 1 Klinefelter s syndrome with female nuclear sex and gynaecomastia (Cases 1–4)
Fig 2 Klinefelter s syndrome with female nuclear sex and minimal clinical stigmata. (Cases 5–8)
Fig 3 Oral mucosal smear in Ca e 1 Nuclei show typical masses of sex chromatin adjacent to nuclear membrane. Cresyl-echt violet × 650

PLATE 2

Fig 4 *Ovoid structure in immature seminiferous tubule in a case of chromatin positive micro-orchidism* H. and E × 160

PLATE 3

(All magnifications × 105)

Fig *a* *Normal testicular biopsy Masson.*
Fig *b* Testis in chromatin positive micro-orchidism Leydig-cell hyperplasia ghost tubules (lower right) and a few small tubules without germ cells. Masson
Fig *c* Testis in chromatin positive micro-orchidism Elastic fibres present around Sertoli-cell-only tubule but absent from ghost tubules Weigert.
Fig *d* *Testis in chromatin positive micro-orchidism (Case 1) All tubules are completely hyalinized* ghost *tubules* Masson.
Fig *e* Testis in chromatin positive micro-orchidism This specimen shows no evidence of tubular hyalinization. Masson.
Fig *f* Testis in chromatin positive micro-orchidism (Case 6) Apparent invasion of seminiferous tubule by Leydig cells. Masson.

PLATE 4

(All magnifications × 105)

Fig *a* Testis in chromatin-positive micro-orchidism. (Pre-pubertal boy aged 14.) Right testicular biopsy For description see text, p 176 H. and E
Fig *b* Testis in chromatin positive micro-orchidism (Pre-pubertal boy aged 14.) Left testicular biopsy For description see text p 176 Masson.
Fig *c* Testis in chromatin positive micro-orchidism. (Post pubertal boy aged 14) For description see text, p 176 H. and E.
Fig *d* Testis in chromatin negative micro-orchidism Tubules showing absence of germ cells and diffuse increase of Leydig cells. Masson.
Fig *e* Testis in presumed case of testicular atrophy Very marked peritubular fibrosis. Masson.
Fig *f* Testis in presumed case of testicular atrophy Persistent elastic tissue in ghost tubules Weigert.

PLATE 5

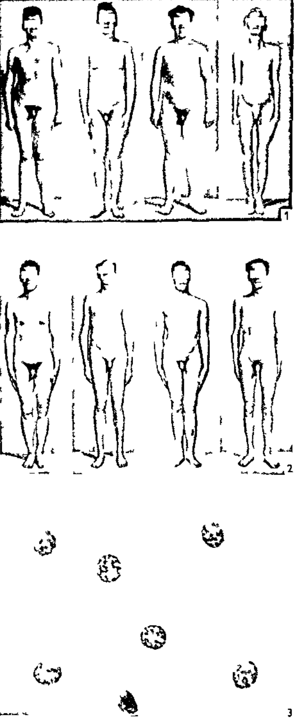
(For description see text below)

Fig 1 Photomicrographs of testis of Case 1 × 100
Fig 2 Case 2 × 140

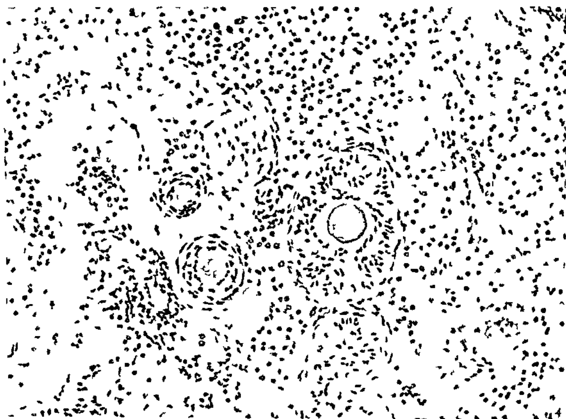
COMMENT

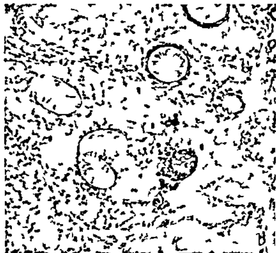
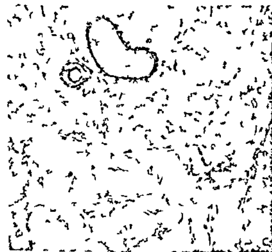
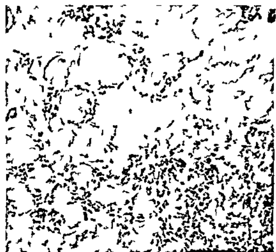
Armstrong Lennox and Ferguson-Smith have described the histology of the testis in chromatin-positive cases of Klinefelter s syndrome The testis presents a characteristic picture apparently found in all cases but I should like to show you that similar histology of the testis has been found in two cases that are not of Klinefelter s syndrome (1) A case of true hermaphroditism which I in collaboration with J E Gray and R. R Race published recently [*Brit med J* 1957 2 605] This case is chromatin-positive and has the polymorph nuclear picture of Klinefelter s syndrome Appearance of a testis section is shown in Plate 5 fig 1 (2) A case of a man of 50 years who was found at operation by Mr P H Dickinson to have a uterus and one undescended testis of unusual appearance The descended testis which was in the scrotum has typical chromatin-

PLATE I



(F g p 180)



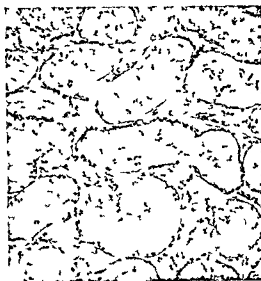




(a)



(b)

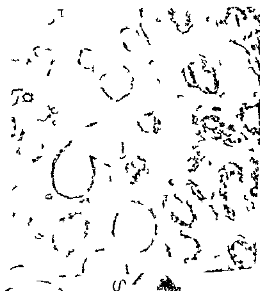


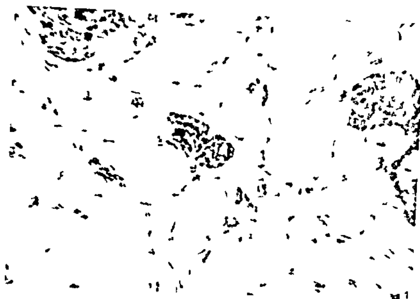
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(d)









positive Klinefelter s histology (Plate 5, fig 2) but the man is chromatin-negative in oral-mucosa and blood films This case has not as yet been published

Thus, three conditions have been described that show the same histology of the testis chromatin-positive Klinefelter s syndrome chromatin-positive true hermaphroditism, and the chromatin-negative case with uterus The characteristic histological picture therefore cannot be due to the presence of X X-chromosomes The two cases that were not Klinefelter s, one chromatin-positive and the other chromatin-negative, both had a uterus

J E Gray has suggested to me that it is possible to bring the three conditions together by making certain assumptions that are not improbable in themselves and resemble mechanisms proved to exist in *Drosophila* (1) In *Drosophila* the Y-chromosome contains genes necessary for maturation of spermatocytes [C B Bridges *Genetics* 1916 1 1 G A Lebedeff, *Proc nat Acad Sci Wash* 1934 20 613] I suggest that Y is absent in *all three conditions which explains the histology of deficient spermatogenesis and* tubular atrophy (2) Lebedeff in 1934 (loc cit) described a gene 1x in *Drosophila* that produces male morphology in X X insects (X X 1 x) I suggest Klinefelter s syndrome *and my case of true hermaphroditism are due to a similar genetic mutation* (3) Lebedeff also found the presence of ovarian tissue when there was simultaneous presence of a gene modifying 1x I suggest therefore, that X X true hermaphroditism is due to the simultaneous presence of a modifying gene to the gene 1x (X X 1x S)

To explain the third condition the chromatin-negative man with uterus one must assume that the normal Y chromosome contains genes antagonistic to X on a non-pairing part of the chromosome If this is so then the loss of Y could result in a lesser total of masculinizing factors (assuming normally some on Y and some on autosomes) the single X would be insufficient to prevent the formation of a testis but would delay it sufficiently long for the Mullerian-duct system to become established as a definite organ I suggest that this man is X O his father s spermatozoa having lost Y or X at spermatogenesis

Lennox The testicular feminization syndrome is most complex with many problems that have not yet been touched on during this meeting The mode of inheritance is remarkable for one thing There are associated defects, such as the lack of body hair which need explaining Wilkins school claim that there is an insensitivity to testosterone, which does not induce the growth of body hair they believe that the condition is not due to an abnormal hormone but to a defect in sensitivity of the target organ Clearly a great deal more work is needed Ultimately we are in the hands of the biochemists when they can measure the hormone output of these abnormal testes completely we will presumably know most of the answer

Assuming the abnormality lies in the secretion by the testis of a feminizing hormone it seems to me there is an argument here against Professor Jost s view that the foetal and adult hormones secreted by the gonads are entirely different Here we have a case where the foetal-evocator action of the gonad and the adult endocrine states are both abnormal and both in exactly the same way—female activity by a male gonad—and this is easier to accept if the same thing is happening each time

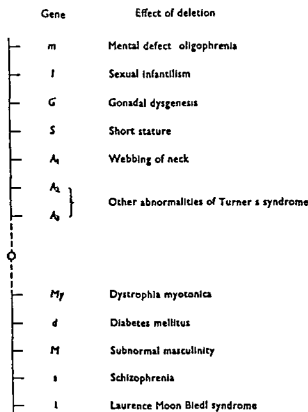
AETIOLOGY OF INTERSEX STATES

By J S S STEWART

Hoffenberg & Jackson [1957] suggested that the variable clinical picture in Turner's syndrome could be explained by involvement of three closely linked genes They designated these genes A (abnormalities of cutaneous cardiovascular and other systems) 'S (short stature) and I (sexual infantilism) It is possible that the last is further divisible into 'G' for gonadal dysgenesis and 'I for sexual infantilism or absence of secondary sex characters perhaps due to failure of cortical development Three cases that I have seen recently are of interest The first is an example of pure gonadal dysgenesis with male nuclear sex but no other stigmata of Turner s syndrome due perhaps to involvement of two genes (G + I) The second is a case of gonadal dysgenesis with male nuclear sex primary amenorrhoea, and short stature without other stigmata This could be due to involvement of three genes (S + G + I) This patient was colour-blind due to extreme deuteranomaly and the defect was present also in a brother and a maternal cousin Both parents had normal colour vision Since a genetic (X X) female must have a father with the same type of colour-blindness this is good evidence that the patient has only one X-chromosome The third patient had the webbing and short stature typical of Turner's syndrome but fairly good breast development was present and regular and apparently normal menstruation had occurred during 6 years The nuclear sex was male This complex could be due to involvement of three genes (A + S + G) The facts reported by Hoffenberg & Jackson [1957] and the cases described here suggest that the linear arrangement of the genes postulated is A S G I

I have previously suggested [Stewart Izatt Ferguson-Smith Lennox & Mack 1958] that Klinefelter s syndrome might be due to a quantitative defect involving the autosomal masculinizing gene M A feminizing gene F is carried on each X-chromosome so that the normal male is M M F and the normal female M M F F Chromatin-positive Klinefelter s syndrome may be due to triplication of the M gene in a genetic (X X) female M M M F F The chromatin-negative variety could be due to deletion of one of the normal M genes in a genetic (X Y) male M F I have also suggested [Stewart 1957] that the defects in these two syndromes of Turner and Klinefelter could be due to inversion crossover The centromere-including type of inversion crossover would probably be most common and two types of crossover chromatids would result One would have duplication of terminal loci at one end and deletion of terminal loci at the other end duplication deficiency The other would have a corresponding deficiency duplication involving the same loci A centromere-including inversion could perhaps lead to deletion of both ends of the chromosome A centromere-excluding inversion could bring subterminal loci into a terminal position or terminal loci into a subterminal position so that subsequent deletion of the terminal segment due to a centromere-including inversion would sometimes lead to deficiency of genes not usually lost and

at other times genes usually lost would be preserved More rarely, compound or multiple inversions or homozygous centromere-excluding inversions with a common segment, could lead to complex deficiencies and duplications There is of course cytological evidence for the occurrence of inversion crossover in man A tentative chromosome map (Text-fig 1) can be constructed to show the possible relative positions



Text fig 1 Hypothetical chromosome map showing the relative position of normal genes. Deletion of these leads to the defect indicated Defects may be dominant (capital letters) or recessive (small letters)

of normal genes whose deletion leads to the defect indicated Some defects would be dominant (capital letters on map) and others would be recessive (small letters) Recessive defects would be manifest only if the same gene on the other chromosome was also abnormal The configuration shown is capable of explaining the following facts reported in the literature

1 The occurrence in a sibship of

(a) Chromatin-positive and chromatin-negative varieties of Klinefelter s syndrome

(b) Klinefelter s syndrome and Turner s syndrome

(c) Turner s syndrome and the Laurence-Moon-Biedl syndrome

In each example one affected member of the sibship could be the product of duplication deficiency and the other of deficiency duplication

2 The association of chromatin-negative Klinefelter's syndrome with
  (*a*) Laurence-Moon-Biedl syndrome
  (*b*) Dystrophia myotonica
  (*c*) Schizophrenia
  (*d*) Diabetes mellitus
  And the association of
  (*e*) Turner s syndrome with oligophrenic mental deficiency
  Association could be due to deletion of adjacent loci Frequency of association would be greater with a dominant than a recessive defect and with closer linkage

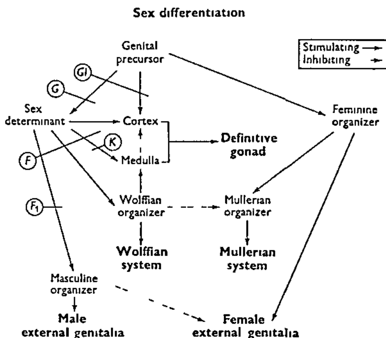
3 The association of chromatin-positive Klinefelter s syndrome with oligophrenic mental deficiency Association could be the product of a centromere-including inversion with duplication of one locus M and deletion of the other m

4 The association of
  (*a*) Turner s syndrome and dystrophia myotonica
  (*b*) Chromatin-positive Klinefelter s syndrome and dystrophia myotonica
  (*c*) Klinefelter s syndrome and Turner s syndrome stigmata in a phenotypical male
  (*d*) Dystrophia myotonica and diabetes mellitus
  Association could be the product of complex inversions

The hypothesis can be tested for it can be used as a basis for some predictions An association of chromatin-negative Klinefelter s syndrome both with schizophrenia and with diabetes mellitus can be predicted and there will also be an association of Turner s syndrome and variants of gonadal dysgenesis with oligophrenia I have been able to confirm an association between chromatin-negative Klinefelter's syndrome and schizophrenia but the incidence has not yet been established It can however be predicted that the incidence of schizophrenics among cases of chromatin-negative Klinefelter s syndrome will equal the gene frequency of schizophrenia if the gene s lies distal to the masculinizing gene, M and is deleted with it The same considerations apply to diabetes mellitus although the gene involved d probably lies between that for masculinization (M) and dystrophia myotonica (My) Thus one should look for cases of chromatin-negative Klinefelter s syndrome among diabetics The incidence of oligophrenic mental deficiency in chromatin-positive Klinefelter s syndrome can be similarly predicted as equal to the gene frequency if the mechanism is that of inversion crossover and the gene for oligophrenia m, lies near to the end of the chromosome It is also possible that associations may exist of chromatin-negative Klinefelter s syndrome with oligophrenia and of gonadal dysgenesis with both schizophrenia and diabetes mellitus due to deletion of both ends of the chromosome but the frequency of this may be too low for detection of an association with a recessive It is possible that many of the defects associated with Turner's syndrome (webbed neck micrognathia shield chest coarctation of aorta skeletal abnormalities epicanthic folds high arched palate deformities of ears duplication of ureter and others) may be genetically determined at separate loci. Analysis of a large series of cases should lead to mapping of the subterminal segment of the chromosome There is already evidence that webbing [Rossi &

Caflisch 1951] and abnormalities of ears and ureters [Hilson 1957] can be inherited as autosomal dominant defects The gene for webbing would seem to lie close to that for short stature The excess of genetic (XY) males could be due to the presence of a sex-controlled lethal factor perhaps fairly closely linked to the factor causing coarctation of the aorta Other factors controlling development may lie on the same chromosome Thus skeletal abnormalities may provide a link with the Klippel-Fiel syndrome high arched palate with Marfan s syndrome and deformities of ears and ureters with renal agenesis

Such a hypothesis has as its corollary a scheme of gonadal development based on the principles of biochemical genetics (Text-fig 2) Interruption at one level (GI) could lead



Text fig 2 Hypothetical scheme of sex differentiation. Suggested levels of block in gonadal agenesis (GI) in gonadal dysgenesis (G) in the normal female (F) in testicular feminization (F_1) and in the Klinefelter syndrome (K) are shown.

to gonadal agenesis due to involvement of appropriate genes Partial block at the same level (G) could lead to gonadal dysgenesis In the normal female a block (F) is assumed to exist and to be due to supremacy of the feminizing factors on the X chromosomes A partial block (F_1) due to involvement of one of these feminizing factors could occur in a genetic (XY) male to cause the testicular feminization syndrome perhaps due to duplication of a segment of the X chromosome in consequence of inversion crossover In congenital adrenal insufficiency [Prader & Siebenmann 1957] a similar block may occur An abnormal stimulus of exogenous (virilizing tumour or hormones in pregnancy) or endogenous origin (adrenal virilism) may cause virilization at this level In Klinefelter s syndrome however the level of action seems to be the same as that of the M/F mechanism but due to involvement of M loci In the chromatin-negative variety the

genetic constitution MF, may be insufficient for complete masculinization so that a partial block (K) may occur and cause incomplete medullary development In the chromatin-positive variety, the genetic constitution M M M M F F may have a similar effect Masculinization of the female may be present but not quite complete The normal block in the female may be removed except for that part (K) necessary for complete medullary development

I prefer a scheme of nomenclature based on the cortico-medullary balance theory of gonadal differentiation and in such a scheme the Klinefelter syndrome is called medullary dysgenesis An extension to include most intersex states is possible [Stewart 1958] In the case reported by Ashley & Jones [1958] similar to the case just described by Dr Jackson there would appear to be a block of the normal female type present in a genetic (XY) male These cases would appear to be examples of cortical dysgenesis

This hypothesis is of course frankly speculative but the inherent difficulties of human genetics justify the presentation of such hypotheses The present one can be tested and had been elaborated in sufficient detail for this to be done

SUMMARY

Evidence is presented for a linear order of the genes causing Turner s syndrome in man It is suggested that the genetic defects in the syndromes of Klinefelter and Turner could be produced by inversion crossover and that the genes involved may lie on the same chromosome A hypothetical chromosome map is constructed and a scheme of sex differentiation based on the principles of biochemical genetics is proposed The hypothesis is capable of proof and is elaborated in sufficient detail for this to be done

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PROFESSOR E C AMOROSO F R S

Chairman s closing remarks

After two days of the most pleasant—and at times excited—deliberations this symposium on Sex differentiation and development has reached a stage where in accordance with the traditions of our Society I must sum up the proceedings and endeavour to bring into relief the main points of agreement and disagreement that have emerged during our discussions In doing so I shall indicate to you to what extent my education on the biology of sex has been improved and to what extent it has not proceeded as far as it might well have done If therefore any part of this summary fails in its allusion to major points whilst emphasizing minor ones unduly you must ascribe this to my own shortcomings and not to any departures from the strict neutrality that is customarily associated with a chairman s functions

At the outset we can all agree that this symposium has fully lived up to the expectations to which it had given rise and that it has amply justified the efforts of its organizer Dr Austin To him as well as to the participants we give our grateful thanks Those who have contributed have spoken with authority and in general to the point but no one present can fail to have been impressed with the scope and interest of the narrative as this was unfolded in the successive papers which ranged from caste differentiation in the honeybee to gonadal dysgenesis in man But the collation of all this information has at the same time revealed how extensive are the gaps that remain in our knowledge This was amply demonstrated by Dr Dodd who cautioned us early in these proceedings that while there are about 20 000 teleost species genetical researches have been limited to only a few species belonging to three genera of the cyprinodonts Likewise we all recall the vigour with which Professor Klein asked what do we know about the nature of X- and Y-*chromosomes in man? But even though I am not prepared to go the* whole way with Professor Klein there is I believe some justification for his pessimism Thus to mention one feature only although it is now well established that the sex chromatin in somatic nuclei serves as a distinguishing mark of chromosomal sex much more detailed cytological studies are required to substantiate the concept that the sex chromatin in these cells is composed of portions of an XX-chromosome pair

One type of evidence was that provided by Dr Butler who gave us a most fascinating account of sex determination and caste differentiation in the honeybee He recalled for us that femaleness in the honeybee could be induced by supernumerary spermatozoa and that the presence of the queen sufficed to inhibit gonadal development in other females and this through the agency of an external hormone contained in the so-called queen *substance These and other facts that Butler presented pose fascinating problems* and indicate that sex determination in this insect is not as simple as it sometimes seems or is made out to be Moreover it gives some force to Professor Peacock s assertion that the theory of sex determination in the two hymenopterans discussed by Dr Butler cannot be applied without modification to other parthenogenetic invertebrates

While certain unequivocal instances of endocrine mechanisms in the invertebrates have been established our knowledge of these processes appears rather incomplete in comparison with the better known phases of vertebrate endocrinology However when one appreciates the difficulties inherent in experimentation with the invertebrates and considers that relatively few investigators devote their efforts to this aspect of biology the investigations of Dr Carlisle assume a new importance—and as Dr Parkes put it inspire confidence that we are on the threshold of many exciting discoveries

These studies of Carlisle suggest that reproductive functions in certain crustaceans are influenced in some manner by the secretions of the androgenic gland a structure that lies adjacent to the vas deferens They indicate moreover that while castration is without effect on the development of the secondary sex characters, removal of the Y organ before puberty results in retardation of gametogenesis as well as suppression of sex characters There is thus substantial evidence that the Y organ is an endocrine structure Present information does not permit a statement regarding the final derivation of the androgenic gland or the Y organ But if as with all the known endocrine glands of the Crustacea the Y organ is demonstrated to be of neural origin this would suggest that the central nervous system of these invertebrates in common with that of the vertebrates is the source of a gonadotrophic principle a circumstance that may have evolutionary implications

Genetic sex determination was a central theme in the contributions of a number of speakers From Dr Dodd s analysis it emerges that a chromosomal basis for sex inheritance can be demonstrated in teleost fishes In some e g *Lebistes* there is an XX XY sex-determining mechanism with male heterogamety whereas in others e g *Xiphophorus* which show a similar chromosomal sex-determining mechanism it is the female that is heterogametic whilst the male is homogametic It is abundantly clear therefore, that the mechanism of sex determination in these cyprinodont fish has a great deal of theoretical interest and as we were reminded it is probable that the mode of evolution of the dual genetic mechanisms for sex determination in vertebrate animals may eventually be solved by careful study of sex linkage in the poeciliid fishes

Proceeding from the assumption that the basic sex-chromosome situation in mammals is XX XY Dr Beatty reminded us that there were nevertheless examples of XX XY_1Y_2 and XX XO mechanisms From his analysis it also became clear that the mode of interaction of sex chromosomes autosomes and cytoplasm in mammals is unknown But in spite of these limitations he argued that if special information became available from intersexes we might then be in a position to decide if the classical *Drosophila* story applies to mammals as well that is to say if sex is determined by the ratio of X chromosomes to autosomes

I pass now to a consideration of the papers on the Origin and development of oocytes in foetal and mature mammals and the Dynamics of the orthotopic ovarian graft' The first of these was discussed by Sir Solly Zuckerman who boldly and appropriately opened with an account of the germinal epithelium and the manner in which it is implicated in the origin of and as a source of the gonocytes He argued that the regenerative capacity of the germ cells was poorly developed and regarded

any evidence for the continuity of oogenesis in the life of mammals and probably in birds also as worthless

Dr Parkes and Miss Parrott dealt with a different aspect of cytogenesis They employed the method of orthotopic grafts to provide the most elegant demonstration of the viability of ova in ovaries previously frozen Their studies are as valid a demonstration of cellular differentiation as it has been my privilege to see and I await a further instalment But meanwhile we must salute the pioneers

In the discussion on The possibility of controlling sex ratio at conception', we were reminded that what we are looking for is essentially a phenotypic difference between X- and Y-bearing spermatozoa which we can utilize for separating them and Dr Marcus Bishop's analysis was as direct an attack on the problem as can now be made It is of course conceivable that the alteration of the primary sex ratio which Bishop thought might be brought about by unequal production of X- and Y-spermatozoa or by their selection in the female tract could be associated with deviations in blood pH as was suggested by Dr McWhirter On the other hand Dr Lewin s results on electrophoretic separation are not convincing for although he claims to have achieved a separation into two components the nature of these fractions was not disclosed It is possible however that they might be separated immunologically in which case a small number of pure X-sperm might as Beatty put it be a key reagent

The material presented by Dr Hayes is so new that it should cause little surprise if many of the interpretations of the phenomena described are modified as new knowledge becomes available Nevertheless it seems to me that the idea of sexuality in bacteria is so important that we must be grateful to him for his description even in its incomplete form The widely ritualized process of meiosis appears to be almost essential in complex organisms Simpler ones find simpler methods adequate and a bacterium is so simple that a new one made up with some spare parts from another has a reasonable chance of living Indeed something corresponding to a gene may be taken up by a bacterium and become replicated in the manner of a hereditary character But to me one of the most fascinating aspects of Hayes work is his observation that certain strains of bacteria can still act as parents or as donors after killing that is to say when so damaged that they can no longer divide If therefore we homologize the donors with males which is an obvious idea we shall have to say that in some bacteria maleness behaves as a contagious disease! In fact bacterial recombination resembles sexual reproduction in some ways and transduction in other ways

Integumentary sex characters in vertebrates was the subject of the paper by Dr Harrison Matthews His was an elaborate description of a problem complementary to the intensive analysis of Professor Klein We were told that these secondary sex characters are more highly developed and diversified in birds than in the other vertebrate classes and that the ornamental sex characters in birds such as the dimorphic differentiation of feathers and head furnishings are physiologically conditioned and serve to bring the sexes together during the reproductive periods I had hoped that we would have been told much more about the factors involved in the control of these characters but in this I was disappointed

One of the difficulties is undoubtedly the fact that the controlling mechanisms vary with the species and breed of bird It is known for example, that in the English sparrow and certain other species sexual differences in the plumage appear to be genetic and autogenous, and that gonadectomized individuals retain the plumage characteristic of the sex, whereas both genetic and hormonal factors are involved in the control of plumage dimorphism in the pheasant On the other hand, in the African weaver finches both hypophysial and gonadal hormones co-operate in the differentiation of plumages whereas hypophysial gonadotrophins rather than gonadal hormones act *directly to control the rhythmic changes in the plumage cycles of the* orange weaver

The possible effects of hormones upon maternal reactions are extremely difficult to analyse This difficulty is due in part to the fact that we know very little about the nature of the adequate stimulus to such behaviour and in part to the failure to recognize the importance and complexity of the endocrinological and psychological side of the picture As Professor Klein reminded us the investigator who concludes that maternal responses in the rat depend upon a given hormone because such responses appear in females that have been placed with new born young and then treated with the hormone, should take into account the fact that psychological factors deriving from contact with the young may elicit the same parental reactions in the absence of hormone treatment This simple truth should be self-evident and I would feel apologetic in recalling it here save for its frequent and flagrant violation by some students of this type of problem

The discovery and application of a ready method of assessing the sex-chromosome status were most ably reviewed by Dr Lennox they have led to the definition of two newly recognized forms of intersexuality gonadal dysgenesis in chromosomal males in which the phenotype is female—Turner s syndrome and seminiferous-tubule dysgenesis in chromosomal females in which the phenotype is male—Klinefelter s syndrome These were discussed by Professor Jackson Dr Peter Bishop and Dr Ferguson-Smith From their accounts it emerges that gonadal dysgenesis and seminiferous-tubule dysgenesis called by Ferguson-Smith primary micro-orchidism can affect either chromosomal males or females though in gonadal dysgenesis there was a greater frequency of chromosomal males As a result we were cautioned to regard as intersexes only those individuals in whom chromosomal sex is contrary to the phenotypic sex

In considering the significance of the greater frequency of chromosomal males in cases of gonadal dysgenesis we were reminded during our discussion of Professor Jost s suggestion that a proportion of patients with gonadal (ovarian') dysgenesis might be chromosomal males who had been feminized in the absence of embryonal testes and their masculinizing hormone or inducer Jost it will be recalled, found that removal of the foetal ovary did not hinder differentiation of a female genital system whereas absence of the foetal testis and its morphogenetic hormone during an early critical period prevented the differentiation of Wolffian derivatives and resulted in entirely female development of the Mullerian ducts urogenital sinus and external genitalia It is thus evident that a foetal testicular substance is essential for differentiation of male sex structures for retrogression of the Mullerian ducts and to prevent the inherent tendency of the foetus to be feminized But we are as yet uncertain of the nature of

this foetal testicular secretion and, until we can apply modern biochemical techniques to its characterization there is little doubt that our knowledge of the mechanism of human sex differentiation will remain incomplete It is clear, moreover that detailed studies of the sex chromosomes in intersexes may reveal in some instances an unusual sex-chromosome complex such as XXY or XO In addition we have Dr Stewart s ingenious suggestions on the influence of autosomal genes

From these various facts and considerations there is no doubt that the sexuality of the individual is determined by genetic constitution but it is also known that many factors may operate during the differentiation of the genital complex to modify or even to reverse the genetic matrix of the developing organism Indeed sexuality like such processes as growth metabolism, menstruation and parturition is the consequence of a system of physiological balances and hence cannot be accounted for on the basis of any single factor Investigators of sex physiology cannot isolate a particular factor and study it singly a complicated system of delicately balanced forces has to be unravelled Unfortunately we have not found an acceptable hypothesis as yet that will bring the various findings into a common explanation. Among higher organisms there is no problem more vital and fundamental than that of sexuality yet there is none in which human society continues to display more ignorance and none in which it is so unwilling to discard preconceived notions

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